

The Journal welcomes letters to the editor. If found suitable, they will be published as space allows. Letters should be typed double-spaced, should not exceed 400 words, and are subject to abridgment and other editorial changes in accordance with Journal style. All letters that reference a recently published Journal article are sent to the original authors for their reply. If no reply is published, the authors have not responded by date of publication.

CLINICAL RELEVANCE

To the Editor:

It is with great satisfaction that I write this letter since for many years I have been critical of the Journal for its lack of clinical relevance in many of its articles.

Over the last few months there has been a significant change in the Journal as exemplified by the article by Toffler and colleagues (Toffler WL, Olenick JS, Wolf NE, et al. *The immunogenicity and safety of intradermal hepatitis B vaccine*. *J Fam Pract* 1991; 33:149-54), where we see family physicians engaged in original clinical research that furthers our understanding of clinical practice and contributes important new information regarding preventive approaches to disease. It is just this kind of clinical research that will carve a legitimate research niche for our specialty and make it easier for the rest of us to continue in our research endeavors.

My sincere congratulations to the authors and the editors who have seen fit to guide the Journal in new and exciting directions.

Ricardo G. Hahn, MD
Department of Family Medicine
University of Tennessee
Memphis

EFFICIENT DIAGNOSIS

To the Editor:

In their recent article, Drs Seller and Lobley¹ comment that "cross-cultural comparisons [of medical care] are difficult to perform and interpret." I would agree with this statement, but even more important, I would agree with something else implied by the article: we can learn a lot about medical care in this country by studying health care in other countries.

As they acknowledge, their study has many methodologic difficulties, including noncomparability

of sampling techniques. In addition, since case selection involved backward tracing from diagnoses to presenting symptoms, the results are probably not an exact reflection of the diagnostic process that occurs in primary care. Their results tell us nothing about the relative cost-effectiveness of the evaluation of patients whose presenting symptoms are not associated with serious diagnoses. What is needed next is a prospective international study of *presenting complaints*.

An important issue that was not addressed in their discussion is that diagnostic interval is only one part of the equation that links onset of patient symptoms with diagnosis, treatment, and outcome. For example, in a study of American patients with colorectal cancer, the time interval between first clinic visit and definitive surgical therapy for health maintenance organization (HMO) patients was three times greater than that for fee-for-service (FFS) patients (47 days vs 14 days).² However, the time interval between onset of first symptoms and initiation of first clinical contact by patients with a variety of cancers was greater for FFS patients than for HMO patients (38 days vs 25 days) from the same practices.³ Time interval from first symptoms to diagnosis and treatment would seem to be a key variable that should be included in future international comparison studies.

David L. Hahn, MD
Arcand Park Clinic
Madison, Wisconsin

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DIABETES SCREENING

To the Editor:

The study by Worrall (*Worrall G. Screening healthy people for diabetes: is it worthwhile?* *J Fam Pract* 1991; 33:155-60) was interesting. I am not sure it was legitimate to use the National Diabetes Data Group plasma glucose level (140.5 mg/dL) on capillary whole blood. Whole blood glucose levels are generally 10% to 15% lower than plasma blood values. I think it would have been more appropriate to use 120 mg/dL (whole blood) as the cutoff for screening. Anyone with a value over that level should have had a serum value determined (140 mg/dL cutoff). Patients in this study who had a capillary reading between 120 and 140 mg/dL (plasma values possibly 140 to 160 mg/dL) were probably missed. Thus, a not-too-sensitive test became even less sensitive. This study probably has a very high false-negative rate, which, of course, could explain the low prevalence rate found in Worrall's sampled cohort.

R. J. Cranston, DO
The Dow Chemical Company
Freeport, Texas

ANDROSCOPY

To the Editor:

I am writing in reference to the article by Wm. Jackson Epperson on androscopy¹ and the accompanying editorial by Drs Patton and Rodney.²

I want to commend Dr Epperson on a very comprehensive study and a well-written article. The major point he emphasizes is the patient

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education value of androscopy.

Family physicians see young female patients at the time of their sports physicals, pre-high-school examinations, etc. These are opportune times to discuss that limiting the number of sexual partners and being monogamous may be the best approach to avoiding cervical cancer. Family physicians also see young male patients. It must be impressed upon them that they can become vectors of the disease. In their editorial, Patton and Rodney state that androscopy is of unproven benefit. I would have to strongly agree with them in an *academic sense*. However, the alternative that I see practiced now is that little or no education is given to men. Men, especially young ones, do not want to go into a gynecologist's office and sit with a room full of pregnant women to hear a rushed 5-minute discussion about human papillomavirus (HPV). Subsequently, girlfriends or wives are asked to relay pertinent prevention information. This is often done in a poor fashion.

If we really are sincere that we, as family physicians, want to prevent

disease, then a half-hour visit is not too long to spend with a man who has been exposed to HPV or who has genital lesions. Perhaps the full androscopy examination is not necessary. However, I strongly believe that the office visit and time for discussion is imperative.

Although Patton and Rodney state that "to date, no link with HPV has been demonstrated" with penile cancer, a recent study from China showed a high association of genital warts on physical examination among patients with penile cancer.³ Another study by Boon concerning penile cancer stated that "it is clear that Balinese men are both vectors and victims of HPV."⁴ The association of human papillomavirus with anal cancer has also been documented in several studies.⁵⁻⁷ Even if penile cancer rates are low, men should be advised to report any non-healing lesions to their physician.

Unfortunately, we do not have all of the answers yet. Prudent medicine at this time, however, would dictate counseling for every male patient who has an HPV infection or has been exposed to HPV. Even if there were no risk factors for men,

they must be informed that their partners must have regular Papanicolaou smears if not colposcopic examinations. Men spread the disease. The scientific, academic proof is not there that treating and resolving the warts makes the situation better. No, is there scientific proof that patient education in this field works (yet). But do we just bury our heads in the sand and ignore the issues? The major emphasis with androscopy should be education!

John L. Pfenninger, MD
Midland, Michigan

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BRIEF SUMMARY

INDICATIONS AND USAGE: LOZOL (indapamide) is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs, and for the treatment of salt and fluid retention associated with congestive heart failure.

Usage in Pregnancy: See PRECAUTIONS.

CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide-derived drugs.

WARNINGS: Infrequent cases of severe hyponatremia, accompanied by hypokalemia, have been reported with the use of recommended doses of indapamide primarily in elderly females. Symptoms were reversed by electrolyte replenishment (see PRECAUTIONS). Hypokalemia occurs commonly with diuretics (see ADVERSE REACTIONS, hypokalemia), and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.

Dilatational hyponatremia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease).

Hypertension may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically.

Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically.

Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.

Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Serum concentrations of calcium increased only slightly with indapamide in long-term studies of hypertensive patients. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.

Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathetic-controlled patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine. In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.


Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II placebo-controlled studies and long-term controlled clinical studies, adverse reactions with $\geq 5\%$ cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; $< 5\%$ cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives,

pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hyperglycemia, hyponatremia, hypochloremia, increase in serum BUN or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities. Clinical hypokalemia occurred in 3% and 7% of patients given indapamide 2.5 mg and 5.0 mg, respectively. In a long-term study (157 patients) potassium supplementation was given to 12% and 27% of patients on indapamide 2.5 mg and 5.0 mg, respectively. Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, bullous eruptions, Stevens-Johnson syndrome, necrotizing angitis, fever, respiratory distress (including pneumonitis), anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription. Keep tightly closed. Store at room temperature. Avoid excessive heat. Dispense in light containers as defined in USP. See product circular for full prescribing information. Revised: June 1990

References: 1. IMS National Prescription Audit (NPA), August 1991. Compared with year-to-date August 1991 percentage growth in new prescriptions among the 10 leading brands of diuretics. 2. Scott-Levin Physician Drug and Diagnosis Audit (PDDA), July 1990-June 1991.

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The preceding letter was referred to Drs Epperson, Patton, and Rodney; Dr Epperson responds as follows:

I greatly appreciate the interest and comments of such an outstanding leader in family medicine as Dr Pfenninger.

The most cost-effective indications for androscopy are as yet unknown. I am in the process of contacting several international experts in this area in an attempt to come up with a practical consensus on the use of androscopy. My feelings are that androscopy is an excellent tool for primary care physicians to use in the diagnosis of male anogenital human papillomavirus (HPV). Once diagnosed, the methods of preventing further spread to women can be discussed with the patient. Without the documentation of this disease through androscopy, the patient will never be fully informed about his disease process.

As Dr Pfenninger reports, the incidence of high-grade penile intraepithelial neoplasia is low, but important. Campion et al¹ found a very high incidence of high-grade penile intraepithelial neoplasia (PIN) in the male sexual contacts of women with high-grade cervical intraepithelial neoplasia (CIN). Carcinoma in situ of the penis was also found in this study of 50 patients. As the incidence of HPV infection continues to grow, we may find that the rare incidence of PIN becomes more prevalent. We will not know this without the use of androscopy. Physicians cannot overlook the importance of screening men at high-risk for PIN just because their personal experiences have found dysplasias to be rare in their

patient populations. Medical literature supports this point in numerous substantial studies.

Our practice of medicine frequently involves the use of common-sense medical advice. Often there is little or no published information available in the academic medical literature to support it. Until there are publications available to answer our questions, we must seek out methods of care based on sound medical judgment. In my opinion, it is sound medical practice to identify an infectious disease and try to prevent its spread through comprehensive patient education.

There is no vaccine available for the prevention of HPV, and there is little chance that this will become available in the near future. Prevention is our only means of reducing the spread of this disease. Men with anogenital HPV must be made aware of their contribution to the spread of this cancer-causing virus. Our present methods of patient education have failed to control the HPV epidemic. Androscopy provides a significant tool for the identification and patient education of men exposed to HPV. More primary care physicians need to provide this procedure for their patients.

*Wm. Jackson Epperson
Murrells Inlet, South Carolina*

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Dr Patton responds to Dr Pfenninger as follows:

Dr Pfenninger has long been an advocate of patient education. We admire this and could not agree more with his concern that young men need to know that they can be the vector of a disease that may be associated with an increased probability of cervical cancer. At this time HPV is not known to cause cancer. This

distinction is important.

We agree that devoting 30 minutes to that task is reasonable. We do have some concern about using androscopy to accomplish patient education, believing that it may send a false message, a message that suggests there is an effective medical intervention that can cure a person of the HPV infection.

The HPV-penile cancer link remains questionable. Most of the articles cited by Dr Pfenninger were from selected populations. The articles also presented several confounding factors that make it impossible to assume any cause-and-effect relationship between HPV infection and penile cancer. These factors include race, hygiene, phimosis, sex outside of marriage, and human immunodeficiency virus infection. The science, however, does not preclude such a link being established in the future. If it is established, and if the incidence of cancer of the penis increases to a point that it warrants some form of screening test, an appropriate screening test will need to be identified that will be applicable to large populations, will be cost-effective, and will allow intervention at a stage that will preclude the use of therapies that may severely handicap the person. At this time, when there is (1) no effective treatment for HPV infection, (2) no established link between HPV infection and cancer of the penis, and (3) no evidence suggesting an increasing incidence of cancer of the penis in our population, the use of androscopy to decrease the incidence of carcinoma of the penis or to diagnose carcinoma of the penis at its earliest stages is unwarranted. We, therefore, agree with Dr Pfenninger that education that focuses on ways of decreasing or eliminating transmission of HPV and other pathogens is, and always will be, an important task for all physicians, and especially family physicians.

*Dean Patton, MD
Department of Family Medicine
East Carolina University
Greenville, North Carolina*