

## CORRESPONDENCE


**DISABILITY PAYMENTS AMONG SCHIZOPHRENIC COCAINE ABUSERS**

*To the Editor:* I am deeply concerned that the report by Shaner et al. (Sept. 21 issue)<sup>1</sup> and the accompanying editorial by Satel<sup>2</sup> may further fuel an already acrimonious discussion about the “appropriate use” of publicly derived funds. Have the authors launched us down a slippery slope, with other populations being prohibited from using public funds that might support addiction or harmful behavior in a very small minority? Why shouldn't there be drug tests for others who receive public assistance, enforced healthy diets for the recipients of taxpayer-derived funds, and rigid policing to prevent any diversion of such funds to unhealthy activities? Why shouldn't investigators supported by the National Institutes of Health who use public funds (i.e., federal grants) to support their own tobacco or alcohol addiction be subjected to intrusive monitoring? Should drug screening become part of the grant process? Although it may seem irrational to facilitate cocaine use by schizophrenics, I am concerned that the study by Shaner et al. may provide more data that will be used in a negative manner in an already polarized national debate. Male schizophrenics may be considered an extreme population, but once it is set in motion, the guillotine to end public support for harmful behavior will be difficult to stop.

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1. Shaner A, Eckman TA, Roberts LJ, et al. Disability income, cocaine use, and repeated hospitalization among schizophrenic cocaine abusers — a government-sponsored revolving door. *N Engl J Med* 1995;333:777-83.

2. Satel SL. When disability benefits make patients sicker. *N Engl J Med* 1995; 333:794-6.

*To the Editor:* Both Shaner et al. and Satel suggest that a partial solution to a “government-sponsored revolving door” is to redirect disability payments from recipients to representative payees. The adverse consequences of this type of intervention, however, are numerous and costly. On the basis of my recent experience with patients who have received the dual diagnoses of schizophrenia and substance abuse, examples of these adverse consequences include prostitution; trading prescription medications for street drugs (or for cash to buy street drugs); stealing from family members, acquaintances, or strangers; panhandling; bullying family members or other psychiatric patients; and making deliveries or carrying out acts of revenge (arson, for instance) for drug dealers in exchange for drugs.

Exercising control over patients with dual diagnoses by controlling their money will work only if we simultaneously offer them something meaningful. Negative sanctions must be accompanied by positive rewards for abstinence or else treatment of those with dual diagnoses is doomed. If we cannot give them something better than drugs, why should they give up the drugs?

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*To the Editor:* Shaner et al. ask a narrow question: Is there a temporal association between the receipt of disability payments, the use of cocaine, and symptomatic relapses, as evidenced by the rate of readmission to the hospital? This is similar to asking whether employed men are likely to drink greater amounts of alcohol in the period after payday than at other times. We suggest that, even if the answer is yes, the question is relatively unimportant.

In their discussion, the authors venture far beyond the narrow scope of their study. They suggest that disability pay-

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ments may be a cause of relapses. To establish the causality of this association would require a comparison group of similar patients not receiving disability payments. Such a study would also require evidence of the strength of the association, its repeatability across studies, a clear temporal association, support from experimental studies, and a dose-response relation, none of which are convincingly shown. Instead, what the authors have shown is that people buy more (drugs in this case) at the time of the month when they have more money, which is very different from showing that having money makes people ill. It is therefore premature, and we think hazardous, for the authors to propose a change in national policy affecting Supplemental Security Income.

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The authors reply:

*To the Editor:* All three correspondents raise the same issue — namely, that our article might be taken as a rationale for stopping direct disability payments to needy persons, a change in policy that they believe might do more harm than good. Dr. Feldman refers to the “slippery slope” leading to oppressive bureaucratic intrusions that he fears might ultimately extend far beyond the population we studied. Dr. Geller, apparently writing from personal experience, confirms our speculation that addicted schizophrenics will continue to use drugs despite the appointment of representative payees, funding their purchases not only through panhandling (as we suggested) but through a variety of frightening acts, including crimes and violence to persons and property. Drs. Thornicroft and Susser question the depth of our causal analysis and suggest that a policy change may be “hazardous” in the absence of definitive evidence of a causal association. We, of course, suggested that the current system may be hazardous as well — thus, the dilemma to which we allude in our penultimate paragraph.

These comments provide a welcome opportunity to re-emphasize an important conclusion we drew in our article. “Simply discontinuing the disability payments,” we wrote, “will not eliminate drug abuse and might exacerbate hunger and homelessness. . . . [E]ven payees cannot prevent the use of drugs purchased with funds obtained by other means.” The payee approach must be part of a comprehensive treatment program, including behavioral interventions that reward abstinence. As clinicians working to develop such programs, we view the payee approach not as an end in itself but as an intermediate step toward restoring health and autonomy.

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### TRIALS OF IMPROVED CARE FOR THE ELDERLY

*To the Editor:* In their study of annual in-home comprehensive geriatric assessments for elderly people living at home (Nov. 2 issue),<sup>1</sup> Dr. Stuck and colleagues use multiple imputation to address problems arising from missing data. Multiple imputation is a great statistical innovation for strengthening

inferences when data are missing. However, I think that researchers should either describe the multivariate model used to generate imputed values or at least indicate where readers can obtain such information. Dr. Stuck and colleagues include only a general statement that “the imputed estimates were derived from the known base-line and outcome data, with the use of maximum-likelihood techniques and simulations.” What model was used for the maximum-likelihood techniques? What kind of simulation approach was used? The authors give a reference,<sup>2</sup> which provides an excellent summary of the general methodology but not the methods specifically used by Dr. Stuck and colleagues.

The authors describe only what happened to point estimates of the intervention effect when imputed values were used. Although this may address the issue of potential bias, missing data also add uncertainty to estimates of intervention effects. Multiple imputation can be used to assess this added uncertainty. It would be appropriate for the authors to discuss not only the direction of results in their sensitivity analyses but also the statistical significance of the results.

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1. Stuck AE, Aronow HU, Steiner A, et al. A trial of annual in-home comprehensive geriatric assessments for elderly people living in the community. *N Engl J Med* 1995;333:1184-9.
2. Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley, 1987.

*To the Editor:* Clinical trials need to define explicitly the follow-up periods. However, in some clinical trials this has ethical implications. People in the experimental or intervention group receive special care, sometimes very intensive care. What happens at the end of the clinical trials? How do the patients feel? After the end of the clinical trial their situation has changed forever. The patients know firsthand a different way of treatment, perhaps a better one that they cannot afford by themselves. Must they go back to receiving their “regular medical care” (if they had any)?

In the three-year study by Stuck et al., the intervention group had both annual comprehensive geriatric assessments performed in their homes by gerontologic nurse practitioners and follow-up visits at home every three months. The nurse practitioners were available by telephone.

In the clinical trial by Rich et al. (Nov. 2 issue),<sup>1</sup> the study treatment consisted of intensive education, individualized dietary assessment and instruction, consultation with social-service personnel, analysis of medications, and intensive follow-up after discharge, including home visits and contact by telephone for 90 days after discharge.

Did the patients fully understand that the treatment was experimental and temporary? How were they shifted back to their regular medical care? What impact did the transition have on the patients?

One cannot ignore these ethical questions.<sup>2</sup> Participants in clinical trials of improved care should not be considered disposable.

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1. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *N Engl J Med* 1995;333:1190-5.
2. Lilford RJ, Jackson J. Equipoise and the ethics of randomization. *J R Soc Med* 1995;88:552-9.

The authors reply:

*To the Editor:* As stated by Gervas and Pérez-Fernández, subjects in the intervention group in our study were visited by gerontologic nurse practitioners for a period of three years. Since all the patients continued to receive medical care from their regular physicians, the continuity of medical care was maintained after the end of the project for all subjects in the intervention group. The termination of the project was carefully planned in advance, since most older persons surveyed wished to continue the preventive visits and had developed close relationships with their nurse practitioners. All participants were informed about the duration of the project at the beginning of the study. Before project termination, the project team reviewed each participant's situation to decide whether any special help was needed, such as referral to a community-based agency. In addition, one nurse practitioner continued to be available by telephone (or, in urgent cases, at home) for an additional year after the end of the project, and contact by telephone every six months is being maintained.

Dr. Belin, who helped calculate the imputed estimates for our study, makes interesting points. Multiple imputation has been developed to estimate the effect of missing values on the results of multivariate analyses, since simply excluding missing data from analyses can result in biased estimates because of selection bias. In our study, we had complete three-year follow-up data on survival and health care use, but data on functional status at three years were missing for 12 percent of the subjects. Therefore, the purpose of the imputation analysis was to test whether the finding of a favorable effect of the intervention on functional outcome might be the result of selection bias due to missing information rather than a true intervention effect. To test this hypothesis, three imputed values were generated for each missing functional-status value on the basis of a set of preselected variables. The models used for this multistep analysis are complex and have now been described in detail.<sup>1,2</sup> As stated in our paper, the results of the imputation analysis indicated that missing values did not result in an overestimation but rather in an underestimation of treatment effects on functional outcomes.

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1. Ezatti-Rice TM, Khare M, Schafer JL. Multiple imputation of missing data in NHANES III. In: Proceedings of the Annual Research Conference of the Bureau of the Census, Arlington, Va., March 21–24, 1993. Washington, D.C.: Bureau of the Census, 1993:459–87.
2. Schafer JL. Algorithms for multiple imputation and posterior simulation from incomplete multivariate data with ignorable nonresponse. (Ph.D. thesis. Cambridge, Mass.: Harvard University, 1991.)

*To the Editor:* Drs. Gervas and Pérez-Fernández raise important ethical questions concerning the fate of patients after the termination of a clinical trial. In our study, the patients were informed at the time of enrollment that the duration of the study was 90 days. Throughout this period, all the patients were followed by their regular physicians, thereby ensuring that the continuity of care was preserved after the study was terminated. For patients assigned to the intervention group, continued follow-up by the study team was offered, but fewer than 10 percent of patients indicated a need for further support.

Despite these precautions, we were concerned about a potential rebound increase in readmissions after the termination

of the study intervention. For this reason, all patients were followed for an additional nine months, during which readmissions were carefully monitored. Fortunately, as reported in our paper, not only was there no evidence of a rebound effect, but also there was a strong trend toward a continued reduction in the number of admissions for congestive heart failure during the extended follow-up period. Thus, although we understand the concern of Drs. Gervas and Pérez-Fernández, we believe that the ethical rights of the participants in our study were fully protected.

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### SCREENING FOR PROSTATE CANCER

*To the Editor:* Woolf's review (Nov. 23 issue)<sup>1</sup> of screening for cancer with prostate-specific antigen (PSA) omits important findings. He states that PSA testing could cost billions of dollars but does not mention that treating advanced prostate cancer is far more costly than treating early disease.

Woolf questions the importance of the spread of cancer beyond the prostate gland because extraprostatic extension has been reported in autopsy studies; however, the spread of cancer is associated with bad outcomes.<sup>2</sup> Findings in autopsy series are not representative of those in the general population. It cannot be assumed that a tumor with adverse histologic features in a man killed in an accident would be harmless in a man with a longer life expectancy, who would have an increased probability of cancer progression.

Woolf does not mention that the Food and Drug Administration has approved one PSA assay, in conjunction with digital rectal examination, for the early detection of cancer or that the positive predictive value of PSA testing exceeds that of mammography for breast-cancer screening.

Woolf cites studies of highly selected patients that question the value of treating prostate cancer.<sup>3–6</sup> These studies give little consideration to the need for treatment to prevent suffering from progressive disease, which should be measured along with metastatic rates and deaths from cancer.

Woolf overstates the complications of radical prostatectomy, citing outdated results obtained before or during the learning curve of contemporary radical prostatectomy. These outcomes do not accurately represent what is available to many patients today. Most of the complications can be effectively treated. The institutional variation in outcomes is not a justification for not screening for early detection of cancer. Early detection remains a goal in the approach to most cancers, even though the benefits have not been formally established for many cancers, including prostate cancer.

Before PSA testing was available, prostate cancer was usually detected too late for cure. Consequently, the mortality and morbidity rates of prostate cancer have continued to rise. Since there are no established modifiable risk factors for prostate cancer, the only practical strategy for improving outcomes is early detection and appropriate treatment. If this strategy is effective, outcomes should begin to improve within the next five years.

A complete assessment of PSA screening, with equal scrutiny of the assumptions and quality of data on both sides, suggests that in appropriately selected men, screening will allow the curative treatment of presymptomatic cancers that otherwise would result in morbidity and mortality.

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(My research is supported in part by a grant from Hybritech Inc., San Diego, California.)

1. Woolf SH. Screening for prostate cancer with prostate-specific antigen — an examination of the evidence. *N Engl J Med* 1995;333:1401-5.
2. Wingo PA, Tong T, Bolden S. Cancer statistics, 1995. *CA Cancer J Clin* 1995; 45:8-30.
3. Johansson JE. Expectant management of early stage prostatic cancer: Swedish experience. *J Urol* 1994;152:1753-6.
4. Chodak GW, Thisted RA, Gerber GS, et al. Results of conservative management of clinically localized prostate cancer. *N Engl J Med* 1994;330:242-8.
5. Krahn MD, Mahoney JE, Eckman MH, Trachtenberg J, Pauker SG, Detsky AS. Screening for prostate cancer: a decision analytic view. *JAMA* 1994;272: 773-80.
6. Fleming C, Wasson JH, Albertsen PC, Barry MJ, Wennberg JE. A decision analysis of alternative treatment strategies for clinically localized prostate cancer. *JAMA* 1993;269:2650-8.

*To the Editor:* Woolf's article on PSA screening is well researched and well reasoned. However, his proposal to have physicians fully explain the PSA-screening controversy to patients, assess their preferences, and then let them decide is unrealistic. As a generalist physician who is supposed to put screening recommendations into practice, I am painfully aware of how many issues I am expected to address during a "routine" history taking and physical examination. A partial list includes screening for depression, alcohol abuse, tobacco use, incontinence, sexual dysfunction, physical or emotional abuse, and the desirability of advanced directives. If any of these are issues, I would then need to devote more time to addressing them.

In clinical practice, time is crucial. Woolf's proposal to explain the PSA-screening controversy to patients takes time, and PSA screening is not the only gray area in terms of cancer detection. Shouldn't I also discuss with patients the pros and cons of undergoing mammography before the age of 50, screening sigmoidoscopy, and even testing for occult blood? Neither fee-for-service nor capitated insurance seems eager to reimburse me for implementing each of these recommendations. So I am left with a long list of recommendations and precious little time. The medical community must consider generalists when making recommendations that they are supposed to implement.

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*To the Editor:* I think we are all confused about what to do in regard to screening for prostate cancer. Our patients recognize our confusion in our mixed messages on screening and treatment recommendations. Dr. Woolf advises that "physicians should neither recommend nor discourage PSA testing without, first, ensuring that patients have complete information about potential benefits and risks, and second, determining their personal preferences." Unfortunately, this approach does not help me in terms of giving advice about the PSA test to a healthy 52-year-old man with a normal digital rectal examination.

Currently, no one can differentiate an early prostate cancer that may be a latent cancer from one that is aggressive and clinically important. Until such a thing is possible, I feel a medical and ethical obligation to search for early prostate cancers. There seems to be quite a difference between telling a man who is 80 years old that he has prostate cancer that will probably be unimportant in his lifetime and telling a man who is 52 that he has prostate cancer and that it may or may not be important in his lifetime.

Until someone can clearly tell me the difference between

the two situations, I will follow the American Cancer Society's recommendation to perform a digital rectal examination of the prostate and PSA screening in every man over the age of 50. Then the patient and I can decide when we can stop, since, as Dr. Woolf suggests, "men with a life expectancy of less than 10 years should be advised that screening and treatment are unlikely to be helpful."

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*To the Editor:* Dr. Woolf fails to identify one of the most serious harms resulting from screening for prostate cancer. When we detect prostate cancer early, but it ultimately does nothing to change a patient's outcome, we harm that patient. Screening, by definition, involves healthy people. A man undergoing PSA screening cannot have symptom relief as a result of screening. The discovery of prostate cancer would mean he is no longer healthy. If his ultimate outcome is not improved by changing his status from healthy to sick, he has been harmed. He has had time spent as a healthy man taken away from him. Since three of every five prostate cancers detected in a screening program are not organ-confined<sup>1</sup> and are therefore not curable with current therapies, these men are harmed by PSA screening. If they suffer adverse effects from the diagnostic workup or treatment of their prostate cancer, the harm is multiplied. . . .

Hence, it is certain that at least some men are harmed by PSA screening. Applying the first ethical principle of medicine — *primum non nocere* (first, do no harm) — leads one to the conclusion that PSA screening should not be generally advised before benefit is proved. It is appropriate for a physician opposed to PSA screening to avoid the topic when patients do not request the test. Why should we even indirectly encourage testing known to harm some and not proved to offer a greater likelihood of benefit than harm? Outside of randomized trials of PSA screening, such discussion may well do more harm than good.

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1. Catalona WJ, Richie JP, Ahmann FR, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol* 1994; 151:1283-90.

Dr. Woolf replies:

*To the Editor:* Several of Dr. Catalona's arguments miss the point. That PSA screening has a higher positive predictive value than mammography says little about its effectiveness. The positive predictive value of a test is proportional to the prevalence of the disease being tested for, which is higher for prostate cancer than for breast cancer.<sup>1</sup> The higher positive predictive value may simply mean that prostate cancer is more common in men than is breast cancer in women, not that PSA testing is more accurate than mammography. Moreover, even if PSA screening is more likely to detect a true positive result, the benefit to the patient is only speculative. Clinical trials demonstrate that mammography lowers mortality, but no such evidence exists for PSA screening. Similarly, approval by the Food and Drug Administration of the PSA assay simply means that it can detect prostate cancer.<sup>2</sup> Tests need not improve outcomes to win such approval.

I agree that postmortem evidence of extracapsular penetration or undifferentiated cells does not eliminate the increased risk of progression associated with these findings. Au-

topsy data remind us, however, that adverse histopathological findings are not a guarantee of symptomatic disease. Autopsy studies of men in their 70s and 80s show that men with these findings may live long lives and die of other diseases, free of prostate-related symptoms. Therefore, the histologic findings in tumors detected by PSA screening cannot be cited as "evidence of cure."

Although Dr. Catalona is correct that isolating mortality from morbidity results in an underestimate of potential benefits, the morbidity of screening and treatment must also be considered in judging harms. The data in Table 2 of my article, which he claims are "outdated," were taken largely from studies published in 1993 to 1995. In my article I acknowledge that PSA screening may be cost effective, but we currently lack the data to confirm that it is. Cost effectiveness cannot be determined by simply comparing treatment costs for early and advanced disease.

As a family physician, I share Dr. Hensel's concern about the lack of time for PSA-assay counseling, but patients have too much at stake for physicians to withhold information on these grounds. Counseling of this intensity is less necessary for the other tests listed by Dr. Hensel, because in those cases benefit is more certain and is less dependent on patient preferences. With practice, PSA-assay counseling requires only a few minutes, especially if the patient is also given educational materials. Primary care physicians spend far more time on less useful activities.<sup>3</sup> A few minutes of shared decision making can spare patients unwise choices and reduce costs.<sup>4</sup>

Dr. Budenholzer believes that physicians opposed to PSA screening need not tell patients about the test. Certainly, physicians should not make all tests available to patients, especially those that are ineffective or harmful. In fairness, however, this cannot be said for PSA screening; without better data, no one truly knows whether PSA screening helps or harms patients. With such uncertainty about a leading cause of death, honest disclosure of the options seems appropriate. In settings in which a uniform policy to test or not test is to be implemented, recommendations against routine screening<sup>5</sup> should apply.

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1. Ries LAG, Miller BA, Hankey BF, Kosary CL, Hurray A, Edwards BK, eds. SEER cancer statistics review, 1973-1991: tables and graphs. Bethesda, Md.: National Cancer Institute, 1994. (NIH publication no. 94-2789.)
2. Advisory Panel Chairpersons Meeting of the Medical Devices Advisory Committee. Fed Regist 1993;58(95):29233-4.
3. Luckmann R, Melville SK. Periodic health evaluation of adults: a survey of family physicians. J Fam Pract 1995;40:547-54.
4. Wagner EH, Barrett P, Barry MJ, Barlow W, Fowler FJ Jr. The effect of a shared decisionmaking program on rates of surgery for benign prostatic hyperplasia: pilot results. Med Care 1995;33:765-70.
5. Preventive Services Task Force. Guide to clinical preventive services: an assessment of the effectiveness of 169 interventions. Baltimore: Williams & Wilkins, 1995.

### POLYCYSTIC OVARY SYNDROME

*To the Editor:* Franks (Sept. 28 issue)<sup>1</sup> cites a prevalence of hyperprolactinemia of up to 30 percent in women with polycystic ovaries, yet he does not address the treatment of women with the polycystic ovary syndrome and hyperprolactinemia. Carefully controlled studies, in which multiple blood samples were used to eliminate the effect of stress on prolactin levels, have demonstrated that the frequency of hyperprolactinemia in women with the polycystic ovary syndrome is similar to that in the general population.<sup>2,3</sup> These and other findings<sup>4</sup> challenge the commonly held belief that the polycystic ovary syndrome and hyperprolactinemia are associated

conditions. Therefore, the possibility that the polycystic ovary syndrome and hyperprolactinemia are two separate conditions should be emphasized, since this point may be relevant to the treatment of anovulatory women with the polycystic ovary syndrome. When pregnancy is desired and clomiphene citrate fails to induce ovulation, bromocriptine, alone or in combination with clomiphene citrate, should be tried before more complicated, time-consuming, expensive, and potentially harmful therapies, such as treatment with gonadotropins, are used. Oral contraceptive pills are usually prescribed for anovulatory women who do not desire pregnancy. However, oral contraceptive pills may increase prolactin levels.<sup>5</sup> Therefore, in women with the polycystic ovary syndrome and pre-existing hyperprolactinemia who are receiving such treatment, prolactin levels should be carefully monitored.

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1. Franks S. Polycystic ovary syndrome. N Engl J Med 1995;333:853-61. [Erratum, N Engl J Med 1995;333:1435.]
2. Murdoch AP, Dunlop W, Kendall-Taylor P. Studies of prolactin secretion in polycystic ovary syndrome. Clin Endocrinol (Oxf) 1986;24:165-75.
3. Minakami H, Abe N, Oka N, Kimura K, Tamura T, Tamata T. Prolactin release in polycystic ovarian syndrome. Endocrinol Jpn 1988;35:303-10.
4. Zacur HA, Foster GV. Hyperprolactinemia and polycystic ovarian syndrome. Semin Reprod Endocrinol 1992;10:236-45.
5. Zacur HA. Oral contraceptive pills and prolactin. Semin Reprod Endocrinol 1989;7:585-610.

Dr. Franks replies:

*To the Editor:* Dr. Zosmer makes some important points about hyperprolactinemia in women with the polycystic ovary syndrome. Space did not permit me to discuss in detail the prevalence and management of hyperprolactinemia. I agree that the prevalence of hyperprolactinemia in women with the polycystic ovary syndrome may have been overestimated. In our own series of 211 subjects, 14 (7 percent) were found to have elevated serum concentrations of prolactin, and in most cases, the elevations were modest.<sup>1</sup> Two women with very high levels of prolactin (>250 ng per milliliter) had presented with the estrogen-deficiency amenorrhea typical of hyperprolactinemia.

As far as management is concerned, I agree with the approach outlined by Dr. Zosmer for the treatment of patients who present with clinical features of the polycystic ovary syndrome and moderate hyperprolactinemia.<sup>2</sup> Of course, women with hyperprolactinemia and estrogen-deficiency amenorrhea who happen to have polycystic ovaries will be cared for differently (i.e., with the use of dopamine agonists as the primary therapy).

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1. Franks S. Polycystic ovary syndrome: a changing perspective. Clin Endocrinol 1989;31:87-120.
2. Polson DW, Mason HD, Franks S. Bromocriptine treatment of women with clomiphene-resistant polycystic ovary syndrome. Clin Endocrinol 1987;26:197-203.

### ADVERSE ENDOMETRIAL EFFECTS OF LONG-CYCLE ESTROGEN AND PROGESTOGEN REPLACEMENT THERAPY

*To the Editor:* Treatment with unopposed estrogen is known to increase the risk of endometrial hyperplasia, atypia, and carcinoma, and therefore the administration of a progestogen during hormone-replacement therapy is recommended.<sup>1,2</sup> The

addition of a progestogen may cause unwanted monthly bleeding, changes in mood, and other side effects.<sup>3</sup> To improve compliance during hormone-replacement therapy, various long-cycle regimens of progestogen therapy are used in clinical practice. However, there are few controlled studies of the safety of such treatment as regards the endometrium, and only one study has been carried out for more than two years.<sup>4,5</sup> We present here preliminary data from the Scandinavian LongCycle Study, which was recently discontinued because of the unsatisfactory safety profile of the long-cycle hormone-replacement regimen.

The Scandinavian LongCycle Study was an open, randomized, multicenter trial conducted in Denmark, Norway, and Sweden of 240 women 45 to 65 years old who had been postmenopausal for at least one year (mean [ $\pm$ SD] age,  $52 \pm 4$  years). Half the women received hormone-replacement therapy with an extended cycle of 84 days: 2 mg of estradiol for 68 days, 2 mg of estradiol plus 1 mg of norethindrone for 10 days, and 1 mg of estradiol for 6 days. The remaining women received 2 mg of estradiol for 12 days, 2 mg of estradiol plus 1 mg of norethindrone for 10 days, and 1 mg of estradiol for 6 days (Trisequens, Novo Nordisk, Copenhagen, Denmark). The base-line characteristics of the groups did not differ significantly. Endometrial-biopsy specimens were obtained before treatment and every 12 months during treatment. The planned duration of the study was five years.

Over the course of two to three years of treatment, simple endometrial hyperplasia developed in eight women in the long-cycle group, complex endometrial hyperplasia in six (one also had atypia), and endometrial cancer in one, whereas in the monthly-cycle group simple endometrial hypoplasia and complex hyperplasia developed in one woman each. The atypia was diagnosed after one year of treatment, and the cancer after three years; previous biopsy specimens from both women were normal. The annual incidence of conversion to hyperplasia, atypia, or cancer is shown in Table 1. In all, the incidence of endometrial hyperplasia, atypia, and cancer after three years of treatment was significantly higher in the long-cycle group ( $P = 0.004$  by an exact Kruskal-Wallis test).

These results indicate that long-cycle treatment to replace estrogen and progestogens increases the risk of endometrial

**Table 1. Yearly Incidence of Endometrial Hyperplasia (Simple or Complex), Atypia, and Cancer in Postmenopausal Women Treated with Two Different Estrogen-Progestogen Regimens.**

YEAR OF STUDY	LONG CYCLE	MONTHLY CYCLE
	<i>no. of diseased specimens/ total no. (%)</i>	
1	7/93 (7.5)	0/102
2	0/77	1/90 (1.1)
3	8/73 (11.0)	1/72 (1.4)
All	15/243 (6.2)	2/264 (0.8)

hyperplasia, and eventually that of atypia and cancer, as compared with conventional therapy using a monthly cycle. Therefore, careful monitoring is mandatory during any long-cycle regimen.

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