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Risk Factors for Thromboembolism

To the Editor: Rodeghiero and Tosetto's data (1) are likely to confuse readers who do not realize that the method used by these authors to test for resistance to activated protein C differs from that used in most laboratories. Rodeghiero and Tosetto apparently tested for resistance to activated protein C on undiluted patient plasma, whereas many other laboratories first dilute patient plasma with factor V–deficient plasma. The latter method increases the sensitivity and specificity of the test for the factor V Leiden mutation (1), while reducing or eliminating the influence of such variables as elevated factor VIII levels. Results of testing for resistance to activated protein C that uses this method correlate closely with the presence or absence of the factor V Leiden mutation (2); thus, it is unlikely that these two variables would be independent risk factors for venous thromboembolism.

Eliot Williams, MD, PhD
University of Wisconsin
Madison, WI 53792

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To the Editor: Rodeghiero and Tosetto (1) studied the risk for venous thromboembolism associated with factor V Leiden mutation and with resistance to activated protein C among 15 109 persons 18 to 65 years of age. The factor V Leiden mutation and resistance to activated protein C were independent risk factors for venous thromboembolism and accounted for 6.6% and 5.1% of all cases of this condition, respectively.

In calculating the incidence of venous thromboembolism in persons with factor V Leiden mutation or resistance to activated protein C, the authors attempted to control for confounding factors by excluding certain patient groups or adjusting the regression models. Potential confounding factors included age, sex, pregnancy, oral contraceptive use, trauma or surgery, a family history of venous thromboembolism, factor VIII levels, and anticoagulant use. However, the authors did not adjust their regression models and odds ratios for cigarette smoking, which has been shown to damage vascular endothelium, promote vascular thrombosis, and increase the risk for venous thromboembolism (2, 3). Clinical experience and recent data (4) support the premise that, in a given patient or population, multiple factors, both genetic and exogenous, interact with host antithrombotic mechanisms to modulate the risk for initial or recurrent venous thromboembolism and determine the natural history of treated or untreated disease. Unfortunately, most of the literature in this area suffers from deficiencies in research design, analysis, and interpretation of findings (5).

Future research must focus on prospective studies that carefully control for inherited and exogenous variables, including long-term cigarette smoking, both active and passive. Without such studies, the questions about whom to test and counsel for thrombophilia and how to manage venous thromboembolism, particularly during follow-up of an acute episode, will remain unanswered.

Stephen J. Jay, MD
Indiana University School of Medicine
Indianapolis, IN 46202-5114

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In response: We thank Dr. Williams for his comment on our test for resistance to activated protein C. As he correctly points out, we measured resistance as originally described by Dahlback in 1993 (1). In fact, our investigation began just a few months before the factor V Leiden mutation was described, and we elected not to change our methods during the study. Dilution of plasma samples with factor V–deficient plasma is an efficient way to identify carriers of the factor V Leiden mutation (2), and many laboratories use this "improved" method to avoid the molecular test. Our findings clearly indicate that resistance to activated protein C is not equivalent to the factor V Leiden mutation. Rather, when the original method is used, a substantial fraction (up to 12%) of the population has a phenotype similar to that of factor V Leiden mutation carriers and has a similarly higher risk for thrombosis. Thus, laboratories relying on the modified activated protein C resistance test (or on molecular diagnosis) could miss some useful information.

Dr. Jay states that our results should have also been adjusted for smoking status. Definite evidence that smoking is an independent risk factor for venous thromboembolism is still lacking. Furthermore, in a previous paper we reported that smokers had a slightly higher response to activated protein C than nonsmokers (3). Assuming that smoking is a risk factor for venous thromboembolism, its effect should result in an underestimation of risk in our cohort. Thus, although we appreciate Dr. Jay's comments, we

do not believe that our study results are affected by not controlling for smoking.

Francesco Rodeghiero, MD
Alberto Tosetto, MD
S. Bortolo Hospital
36100 Vicenza, Italy

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Hormone Replacement Therapy in Postmenopausal U.S. Women

To the Editor: I read with interest the article by Keating and colleagues (1), who reported that in a random sample of U.S. adults, women with diabetes mellitus were less likely to have been prescribed hormone replacement therapy (HRT)—findings that, as the authors indicate, are concordant with data from a large patient population in Canada (2).

When we consider a possible interpretation for this apparent "undertreatment" of postmenopausal women with diabetes mellitus, it is noteworthy that a sizable proportion of these diabetic women would be obese or overweight. There are several possible explanations for why obese postmenopausal women seem to be "undertreated" with HRT. First, because the adipose tissue becomes the primary source of endogenous estrogens after menopause, obese women probably enter menopause with a higher level of endogenous estradiol than their leaner peers and therefore may present with fewer symptoms of menopause that would prompt a physician to prescribe HRT. Data supporting a lower incidence of menopausal effects (such as hot flashes or lower bone density) among heavier women were recently reported (3, 4). In addition, physicians may intentionally withhold estrogen replacement therapy among clinically obese postmenopausal women as a preventive measure against hormone-related cancer.

In this context, I pose the following question to Keating and colleagues: Does the lower prevalence of hormone use among diabetic women in the sample you studied also persist among lean women?

Pramil N. Singh, DrPH
Loma Linda University
Loma Linda, CA 92350

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In response: Dr. Singh offers a plausible physiologic explanation why obese women might be less likely to be taking HRT. In our multivariate analysis, we used a waist-to-hip ratio of more than 0.85 as a marker of obesity because central adiposity is strongly correlated with risk for coronary heart disease in women (1) and might be an important confounder of HRT use. However, women with an increased waist-to-hip ratio were not statistically less likely to use HRT than other women.

As Dr. Singh infers, most of the diabetic women in our sample were overweight (78% had a waist-to-hip ratio >0.85 and 68% had a body mass index >27). In additional analyses, compared with nondiabetic women, diabetic women with a normal waist-to-hip ratio and those with a waist-to-hip ratio greater than 0.85 were less likely to use HRT (odds ratio, 0.14 [95% CI, 0.02 to 0.94] and 0.19 [CI, 0.05 to 0.68], respectively). The small number of diabetic patients with a normal waist-to-hip ratio in our sample, reflected in the wide CI, limits our ability to draw definite conclusions for these women as a separate group; however, our data do not support a difference in the use of HRT between lean diabetic women and obese diabetic women.

We have considered two other possible explanations for our finding of lower rates of HRT among diabetic women. First, these women may be taking several medications already, and they or their physicians may wish to avoid additional medications unless absolutely necessary. They may also have more issues to address during medical visits, and time constraints may preclude thorough discussions about the benefits and risks of HRT (2). In addition, physicians may be concerned that estrogen may aggravate glucose intolerance. In one recent study, HRT was associated with small improvements in fasting glucose levels but slightly decreased postprandial glucose tolerance (3). It remains unclear whether our finding of lower rates of HRT among diabetic women represents "undertreatment." A preliminary observational report from the Nurses' Health Study (4) suggested that diabetic women who use HRT have about half the risk for coronary heart disease compared with diabetic nonusers. However, a randomized trial, the Heart and Estrogen/progestin Replacement Study (5), found no benefit of HRT for the secondary prevention of coronary heart disease, even in a subgroup analysis of the approximately 19% of women in the cohort who were diabetic.

Nancy L. Keating, MD, MPH
John Z. Ayanian, MD, MPP
Alan M. Zaslavsky, PhD
Harvard Medical School
Boston, MA 02115

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Thrombolytic Predictive Instrument

To the Editor: As described in an earlier issue of *Annals of Internal Medicine* (1), when programmed into a conventional electrocardiograph, the thrombolytic predictive instrument (TPI) provides the emergency physician with predicted probabilities of key outcomes for a patient with acute myocardial infarction: 30-day mortality, 1-year mortality, and cardiac arrest within 48 hours if the patient is given or not given thrombolytic therapy and intracranial hemorrhage or other major (transfusion-requiring) bleeding if thrombolytic therapy is used. We would like to bring attention to how one variable in one of the TPI's five component predictive instruments should be altered in its use to reflect a recent change in practice.

In the TPI component predictive instrument for thrombolysis-

related major bleeding, the variable for weight-adjusted dose reflects that a person of less weight is more likely to bleed when given a specific thrombolytic dose than a heavier person given the same dose. When the TPI was developed, clinical practice was to give a standard dose to all patients (for example, 100 mg of tissue plasminogen activator). Since then, it has become standard practice to adjust the dose of thrombolytic agent based on the patient's weight, so that smaller patients receive smaller doses and larger patients receive larger doses. Therefore, to accurately predict bleeding, TPI calculations should assume the use of a weight-adjusted dose. This does not require a change in the bleeding predictive model's published variables or their coefficients, but it does change the predictions that should be generated by an electrocardiograph. Accordingly, we suggest that 1) the variable value for the "standard adjusted by weight" be set to 0.3 to reflect the fact that the correction factor to the standard dose, 70 divided by the patient's weight, is now unnecessary (because the standard dose is defined as 1, the variable now equals 0.3), and 2) the electrocardiogram header text should say "with weight-adjusted dose" rather than "with standard dose," as did the example electrocardiogram in our article (1).

Changing from a fixed dose to weight-adjusted dose in the calculated probabilities of thrombolysis-associated major bleeding for patients in the TPI database (1) moves the 95th percentile of predicted probabilities from 23.4%, assuming the fixed dose, to 14.1%, assuming use of a weight-adjusted dose. This reflects the expected decrease in bleeding when lighter-than-average patients are given appropriately weight-adjusted doses, consistent with current practice.

Harry P. Selker, MD, MSPH
Christopher H. Schmid, PhD
John L. Griffith, PhD
New England Medical Center
Boston, MA 02111

Reference

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The Park Nicollet Experience

To the Editor: Having just read the supplement on hospitalists, I am still confused about the place of the hospitalist. Despite little more than anecdotal data on the effectiveness of hospitalist programs, there is an ongoing trend for support of these programs. The impetus seems to be a desire to control costs, although some have mentioned that general internists can no longer manage medical inpatients. This is sad and unfortunate.

The discontinuity of care and disruption of the physician–patient relationship are the most troubling part of this equation. Surveys reporting patient satisfaction with the hospitalist system do not indicate whether the patient has an ongoing relationship with a primary care physician or has been assigned through their health plan and has never seen the physician.

Some groups have reported cost savings (1), but others (2) have not. Savings are assumed to come from decreased utilization, but a false economy seems to be at work. If the Park Nicollet experience (1) is representative, requests for consultations will decrease but the use of "curbside" consultations will increase. This appears to be a similar level of utilization with no billing for services.

It is difficult to maintain competence in many more technical skills without maintenance of a fairly large hospital practice. However, the fundamentals of inpatient medicine remain the same. We still admit, stabilize, diagnose, treat, and attempt to utilize resources wisely. If this requires additional training, so be it.

There is a reason that most hospital-based physicians are internists. There may be room for improvement, but internal medicine can still continue to provide high-quality inpatient and outpatient services. This is based on training and experience. We must maintain our skills through meaningful continuing medical education, by additional training, and by treating our patients in the hospital when they need us. These goals may not be easy, but that is why internal medicine is so rewarding. We should be fighting for our patients and our specialty rather than encouraging services of marginal value. If the training of internists is problematic, we should improve it before we alter the practice of internal medicine. The hospitalist adds little to the care of an inpatient in an urban hospital setting. Dedicated hospitalists may have a place in rural or isolated hospitals, but I suspect that this is not the niche hospitalists wish to fill. Before we superimpose another level of providers between physicians and their patients, we must consider the consequences.

Michael J. Dawson, MD
West Allis, WI 53227

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In response: Patient acceptance was our biggest concern, and we monitored this carefully. One hundred ninety-eight patients discharged between 1 September 1993 and 30 November 1993 (before the implementation of the hospital system) were surveyed with a mailed questionnaire and a reminder postcard. We also sent a subsequent additional mailing to nonrespondents. These persons made up the baseline inpatient group. The identical questionnaire was mailed to 214 patients discharged between 9 January 1994 and 1 March 1994 (just after the start of the hospital service). Finally, 368 patients discharged 18 months after the inception of the hospital service were surveyed in an identical fashion.

Response rates were 68% to 76%. There was no difference in the groups with regard to age, sex, whether they belonged to a capitated health plan, or length of time they had been patients at Park Nicollet. Most were not in a capitated system and were established patients of the clinic. Similarly, there was no difference in their response to 11 additional measures of satisfaction. After getting the same answer on two separate surveys after implementation, we stopped asking the question.

Dr. Dawson also wonders about the economics. Our data indicate the decrease of hospital bill generated, which is independent of the billed charges of consultants and attending physicians. It is undoubtedly true that the physician–patient relationship continues to be important to some patients, particularly those with severe and life-threatening diseases. We must also acknowledge that a significant and growing part of the population would sacrifice that relationship for service, cost, and rapid knowledge.

Richard B. Freese, MD
Park Nicollet Clinic HealthSystem Minnesota
St. Louis Park, MN 55416

Sigmoidoscopy Reimbursement

To the Editor: The article by Lewis and Asch (1) was timely and confirmed my recent experience. I have just opened a community-based family practice office for the Department of Family Medicine at the University of North Carolina, Chapel Hill. In accordance with recommendations for colorectal cancer screening, we wanted to provide office-based screening sigmoidoscopy for our patients. We conducted a break-even analysis, in which we projected our costs and local health maintenance organization and Medicare reimbursement rates, and found that we needed to do approximately seven examinations a month, an estimate very close to that of Lewis and Asch. Our analysis included use of

higher-end equipment; for example, because our department is a teaching site, we wanted a scope with a video monitor.

We concluded, as did Lewis and Asch, that providing screening sigmoidoscopy to our patients could easily be an economic liability. I was disheartened by this result, because I am convinced that colorectal cancer is preventable if proper screening and follow-up are done. Unfortunately, patient adherence to recommendations for colorectal screening is poor, and in our experience, being able to provide the service in the office improves compliance. The insufficient Medicare reimbursement rates for flexible sigmoidoscopy, with and without biopsy, are a disincentive to doing this procedure in the office. As a result of this inadequate reimbursement, fewer primary care physicians offer this screening to their patients, leading to decreased adherence with screening; progression of preventable colorectal cancer, pain, and suffering in patients; and, ultimately, increased costs to Medicare. An increase in Medicare reimbursement rates for screening flexible sigmoidoscopy would make it more feasible to offer this service to patients and would probably result in decreased costs in the long run by preventing colorectal cancer.

Evan Ashkin, MD
University of North Carolina, Chapel Hill
Chapel Hill, NC 27599-7595

Reference

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Splenectomy-Induced Portal Hypertension and Pulmonary Hypertension

To the Editor: Hoeper and colleagues (1) reported that risk for pulmonary hypertension is increased after splenectomy (1). They speculated that the abnormal erythrocytes remained in the circulatory system longer and triggered platelet activation, leading to thrombi in the pulmonary vascular bed.

Other possibilities can be considered. Because splenectomy may cause portal hypertension, which leads to intrapulmonary shunting, portal hypertension plays a role in the development of the hepatopulmonary syndrome in liver disease (2). This syndrome is characterized by hypoxemia in patients with chronic liver diseases and no intrinsic lung disease (3). Because hypoxia is known to have pathogenic significance and elevate pulmonary arterial pressure by means of hypoxic pulmonary vasoconstriction, splenectomy and portal hypertension–related hypoxemia are implicated in the pathogenesis of pulmonary hypertension. The sustained hypoxemia and respiratory acidosis may cause pulmonary vascular remodeling. Abnormalities of arterial oxygenation in the hepatopulmonary syndrome are primarily due to the increased production of nitric oxide (NO) in the lung (3). In an animal model, portal hypertension accelerated angiogenesis and caused structural changes through increased NO production (3). In addition, increased tumor necrosis factor-α and the increased NO production due to portal hypertension could result in oxidant injury. A rat model indicated that *N*-acetylcysteine treatment could prevent the hemodynamic circulation by inhibiting formation of reactive oxygen species (4). Increased production of reactive oxygen species may be another mechanism of remodeling of the pulmonary vascular bed.

However, hypoxia also inhibits NO production in the lung. Thus, splenectomy does not always cause pulmonary hypertension. The reduction and elevation of endothelial NO synthetase expression have been reported in pulmonary vessels of patients with pulmonary hypertension. Particularly high gene expression of endothelial NO synthetase may be identified in the plexiform lesions of these patients (5). The regional distribution of NO synthetase may be important in the development of pulmonary hypertension in patients who have undergone splenectomy or have the hepatopulmonary syndrome.

Although splenectomy may be an important risk factor for pulmonary hypertension, the pathogenic mechanism of pulmonary hypertension may be complicated. Splenectomy-induced portal hypertension and the hepatopulmonary syndrome may play a key role in the development of pulmonary hypertension.

Shinji Teramoto, MD
Takeshi Matsuse, MD
Yasuyoshi Ouchi, MD
Tokyo University Hospital
Tokyo, 113-8655 Japan

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In response: We thank Teramoto and colleagues for their comments. Their suggestions about possible mechanisms for the development of pulmonary hypertension after splenectomy are inconclusive. First, the development of portal hypertension after splenectomy is rare, and coexistence of portal hypertension and pulmonary hypertension was thoroughly excluded by Doppler ultrasonography in all our patients. No evidence suggests that abnormal pulmonary vasodilatation as part of the hepatopulmonary syndrome plays any role in splenectomy-associated pulmonary hypertension. Hypoxic vasoconstriction is not a feature of the hepatopulmonary syndrome, and respiratory acidosis is almost never involved.

Teramoto and colleagues also stressed the role of impaired regional NO synthetase expression for the development of the hepatopulmonary syndrome and pulmonary hypertension. Although increased levels of exhaled NO have been demonstrated with intrapulmonary vascular dilatation (1, 2), the situation is less clear for pulmonary hypertension (3, 4). However, the conclusion that splenectomy does not always cause pulmonary hypertension because hypoxia inhibits NO production (and therefore abnormal pulmonary vasodilation) is not supported by scientific evidence and contradicts clinical experience. Most patients who have had splenectomy are normoxic and will probably never develop pulmonary vascular disease. According to our experience and from the correspondence we received after our paper was published, the risk for pulmonary hypertension after splenectomy seems especially high in patients with hemolytic disorders, such as spherocytosis or thalassemia. Therefore, we think it is reasonable to assume that the prolonged presence of abnormal erythrocytes in the circulation is involved in the pathogenesis of postsplenectomy pulmonary hypertension. The exact mechanism, however, remains speculative.

Marius M. Hoeper, MD
Jost Niedermeyer, MD
Hannover Medical School
30623 Hannover, Germany

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False-Positive HIV Diagnosis by HIV-1 Plasma Viral Load Testing

To the Editor: Rich and colleagues (1) demonstrated difficulties with the use of HIV-1 plasma viral load testing to diagnose HIV infection. We, too, have witnessed false-positive results on testing for HIV-1 with polymerase chain reaction (PCR) in a man presenting with encephalopathy secondary to alcohol withdrawal and hypertension.

A 59-year-old man known to have type 2 diabetes mellitus, alcoholism, hypertension, and chronic obstructive lung disease was hospitalized for headache and confusion. He had no history of trauma, intravenous drug use, sexual promiscuity, homosexual encounters, transfusion, or sexually transmitted disease. Physical examination confirmed disorientation without localizing signs. Magnetic resonance imaging showed increased cerebral atrophy, consistent with the patient's age. Lumbar puncture was normal. Nitroprusside was used to control hypertension. The result on enzyme-linked immunosorbent assay for serum HIV was negative, whereas the result on testing for serum HIV-1 RNA by using reverse-transcriptase PCR was positive (196 copies/mL, log 2.9) (Ultraquant, Roche). Results of repeated enzyme-linked immunosorbent assay of serum and cerebral spinal fluid and PCR assays for HIV RNA were all negative.

The HIV-1 PCR assay was designed to monitor HIV therapy, not to diagnose HIV infection. For diagnostic tests, prior probability of a positive test result needs to be considered. In patients (like ours) with a low prior probability of disease, almost all positive test results are false positive. Our urge to confirm the cause of acute encephalopathy rather than accept a diagnosis of exclusion resulted in inappropriate use of HIV-1 PCR.

This case confirms the importance of prior probability in diagnostic assays. We concur with Rich and colleagues that low-level positive results on HIV-1 PCR must be interpreted cautiously within the context of the patient's entire picture.

Daniel H. Havlichek Jr., MD
Elie Hage-Korban, MD
Michigan State University College of Human Medicine
East Lansing, MI 48824

Reference

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Nosocomial Transmission of Hepatitis C Virus

To the Editor: A 48-year-old-woman referred for acute hepatitis was found to be positive for anti–hepatitis C virus (HCV) antibodies (Ortho HCV 3.0, Ortho Clinical Diagnostic Systems, Roissy-en, France) in February 1994. Recent seroconversion was confirmed by the evolution of antibody profiles tested with a strip immunoblot assay (Chiron RIBA HCV 3.0 SIA, Ortho Clinical Diagnostic Systems). The patient had no history of blood transfusion or drug use.

In December 1993, she had undergone under anesthesia for colonoscopy without biopsy. Seven of the 8 other patients who had had endoscopy (6 of whom had colonoscopy) on the same day could be called back; one patient had died of intestinal cancer. Only one of these patients was found to be anti-HCV positive. This man had had colonoscopy just before the propositus, and his HCV infection was not known at this time. Both patients were infected by HCV genotype 2.

Part of the HCV NS5 domain (nucleotides 7975-8196) was cloned after polymerase chain reaction. Two clones per patient were sequenced and analyzed by using three phylogenetic methods; these clones were compared with a panel of 53 HCV-unrelated sequences retrieved from European Bioinformatics Institute and National Center for Biotechnology Information databanks and from our laboratory (1, 2). The two clones were identical for each patient. The sequences of the two patients differed only by three nucleotides. Phylogenetic analyses showed that both isolates were of subtype 2c and were included in a same branch of the tree.

The main hypothetical source of HCV infection in this case may have been the use of the same colonoscope without adequate disinfection (3, 4) or the use of a multidose anesthesic vial or the same syringe (5). However, other sources cannot be excluded. The gastroenterologist worked with two colonoscopes during this session, and it seems unlikely that two consecutive colonoscopies were performed with the same equipment.

S. Le Pogam
Alain Gondeau, MD
CHU Bretonneau
37044 Tours Cedex, France

Y. Bacq
CHU Trousseau
37044 Tours Cedex, France

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Renin-Secreting Adenocarcinoma of the Colon

To the Editor: We describe what we believe to be the first case of a renin-secreting adenocarcinoma of the colon. A 66-year-old retired schoolteacher presented with a 3-month history of headaches, vomiting, constipation, and weight loss. She had severe hypertension (blood pressure, 210/140 mm Hg) and hypokalemia (potassium level, 2.2 mmol/L). A barium enema showed appearances of cecal carcinoma. Both plasma renin levels (21 pmol/L; normal, 1.1 to 2.7 pmol/L) and plasma aldosterone levels (1010 pmol/L; normal, 100 to 450 pmol/L) were elevated. Potassium supplements and oral spironolactone (100 mg daily) rapidly corrected the hypokalemia, and a calcium antagonist (amlodipine, 10 mg daily) was used to control blood pressure. Abdominal

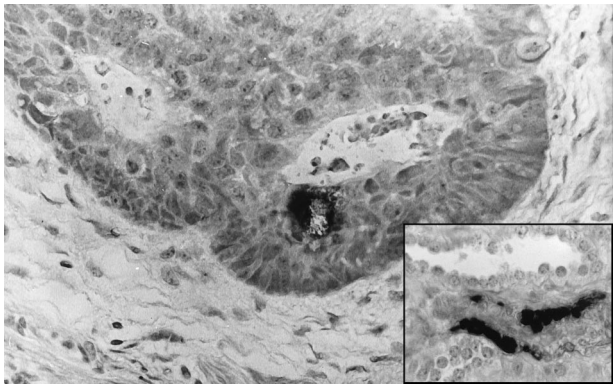

Figure. Light micrographs of a renin in situ hybridization preparation counterstained with hematoxylin. Acini of adenocarcinoma contains a single large tumor cell, which stains strongly positive for renin messenger RNA (original magnification, ×450). The inset shows the positive control section of kidney with renin-positive cells externally situated on an arteriole (original magnification, ×250).

computed tomography showed no renal tumor but demonstrated multiple lesions throughout the liver that were compatible with metastases.

At surgery, a $6 \times 4 \times 3$–cm nodular tumor was found just above the ileocecal valve, with two adjacent small nodules. Histopathologic examination showed a typical moderately differentiated adenocarcinoma with hepatic metastases (T3 N3 M1). In situ hybridization of tumor tissue by using riboprobes made from human renin complementary DNA detected messenger RNA for renin (**Figure**); this confirmed renin-secreting adenocarcinoma of the cecum.

Renin and aldosterone levels remained high after hemicolectomy (renin level, 41 pmol/L; aldosterone level, 2320 pmol/L). Spironolactone was successful in treating the hypokalemia but was not well tolerated because of dehydration and hyponatremia. A synacthen test excluded hypoadrenalism. The angiotensin AT1 receptor antagonist losartan was better tolerated and reduced the requirement for potassium supplements. However, the patient remained significantly hyponatremic (sodium level, 120 mmol/L), which may have been attributable to "pressure natriuresis."

Renin secretion by an extrarenal neoplasm is unusual but has been reported in bronchial carcinomas (1), pancreatic carcinomas (2), and a variety of other neoplasms (3), including adenocarcinoma of the ileum (4). To our knowledge, no previous reports have described a renin-secreting colonic neoplasm.

Tim R. Ringrose
Paddy A. Phillips
The John Radcliffe Hospital
Headington, Oxford OX3 9DU, United Kingdom

George B.M. Lindop
Western Infirmary
Glasgow G11 6NT, United Kingdom

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Famotidine-Induced Erythema Multiforme: Cross-Sensitivity with Cimetidine

To the Editor: Histamine-2 receptor antagonists (H_2 blockers) are widely used to treat gastric ulcers and the hypersecretory syndrome. These drugs are considered to have very few side effects. We describe a patient with erythema multiforme that led to serious generalized exfoliative erythroderma caused by the H_2 blockers cimetidine and famotidine.

In a clinic, a 68-year-old woman had received the calcium-channel blocker efonidipine for hypertension and cimetidine for reflux esophagitis and suspected gallstones. She was admitted to our hospital for detection and treatment of gallstones. Erythema multiforme lesions were noted on the extremities and abdomen. The calcium-channel blocker manidipine and famotidine were initially administered for 4 days. After dermatologic examination to determine causative drugs, famotidine was terminated. On skin biopsy, the eruptions were found to be histologically exudative erythema, but serious generalized exfoliative erythroderma was apparent. Results of tests for drug lymphocyte stimulation were negative. With the patient's consent, cimetidine was administered after a washout period. Erythema multiforme eruptions similar to the initial eruptions subsequently appeared; itching also developed. After a second washout period, famotidine was given again; similar eruptions with itching developed. The calcium-channel blocker manidipine was not found to be a causative agent.

Eruptions caused by cimetidine or famotidine have been noted in only 15% and 16%, respectively, of persons who receive these drugs. Except for a few cases of the Stevens–Johnson syndrome caused by cimetidine (1), serious cases of skin eruptions caused by other H_2 blockers are rare. Famotidine-induced skin eruptions are extremely uncommon, and only a few cases of symptomatic dermatographism (2) and maculopapular eruptions (3) caused by this drug have been reported. Some H_2 blockers have been found to have cross-sensitivity with roxatidine and ranitidine, which produces adverse reactions (4). Cross-sensitivity intermediate to that of ranitidine, famotidine, and nizatidine in maculopapular eruptions (3) has been reported. In our patient, cross-sensitivity intermediate to that of cimetidine and famotidine was confirmed by provocation tests. Other reports have indicated no cross-sensitivity intermediate to that of cimetidine and ranitidine (5). Bossi and colleagues (3) discussed similar structures of the side chains bonded to the ring structures as a possible causative factor. Chemical structures indicated that lateral chains of these drugs, which bonded to imidazol and thiazol rings, had somewhat similar structures, possibly implicating them in development of adverse reactions. Attention should be directed to cross-sensitivity among H_2 blockers.

Yasuhiro Horiuchi, MD
Kazuto Ikezawa, MD
Tsukuba Memorial Hospital
Tsukuba City, Ibaraki, Japan

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Tropheryma whippelii in Synovial Tissue and Fluid

To the Editor: Whipple disease is a systemic infection in which 67% of patients present with articular symptoms (1). These symptoms usually precede diagnosis by a mean of 6 years (range, 6 months to 28 years) (1). The 16S ribosomal RNA (rRNA) of the causal agent of Whipple disease, *Tropheryma whippelii*, has recently been identified (2). Because of this, 16S rDNA primers are now used to detect this organism by polymerase chain reaction (PCR), mainly in duodenal and lymph node tissues (2–4). We have extended this approach to the diagnosis of Whipple arthritis.

A patient with a 28-year history of rheumatoid-like symmetric seronegative destructive polyarthritis developed weight loss, fever, diarrhea, and lymphadenopathy. A diagnosis of Whipple disease was considered on the basis of positive periodic acid–Schiff staining of the duodenal tissue and an epithelioid granuloma of the axillary lymph node. Synovial fluid and tissue samples were obtained by needle puncture. Amplification by PCR was performed as previously described (3); however, digoxigenin-labeled dUTP (Roche Molecular Biochemicals, Grenoble, France) and a specific biotinylated probe were used. *Tropheryma whippelii* was detected by PCR in two samples each of synovial fluid and tissue and in the lymph node specimen. Results of tests on all control specimens were negative. The sequence of PCR products obtained with other primers (4) from synovial fluid and lymph node tissue shared more than 96% sequence identity with *T. whippelii* 16S rDNA (GenBank M87484). Antibiotic therapy led to dramatic improvements.

This is, to our knowledge, the first report of the detection of *T. whippelii* by PCR in synovial fluid or tissue from a patient with

Whipple disease. Whipple disease should be considered a rare but treatable disease in the differential diagnosis of seronegative destructive polyarthritis. Polymerase chain reaction assay using synovial fluid or tissue specimens proved to be a useful diagnostic tool. Our results raise the question of whether patients with unexplained destructive seronegative polyarthritis should be considered for joint fluid or tissue testing for *T. whippelii* by PCR. Further studies are also required to determine whether PCR on synovial tissue or fluid may allow earlier diagnosis of Whipple disease, especially during the early phase, and thereby prevent the development of severe systemic forms of the disease.

Note: Since submission of our letter, a study (5) reported that *T. whippelii* was detected in one synovial tissue sample and one synovial fluid sample in the early phase of Whipple disease (before the intestinal symptoms).

Xavier Puéchal, MD
Radwan Saad, MD
Le Mans General Hospital
72000 Le Mans, France

Jean-Dominique Poveda, MD
Pasteur-Cerba
75015 Paris, France

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Sudden Jaundice with Isolated Atypical Perinuclear Antineutrophil Cytoplasmic Antibodies

To the Editor: A 42-year-old computer programmer presented with jaundice and reported 2 weeks of nonspecific symptoms. Jaundice and hepatomegaly were present. The liver measured 17 cm in the right midclavicular line, and the spleen was not palpable. Serum bilirubin level was 257 μmol/L (15.0 mg/dL) conjugated and 29 μmol/L (1.7 mg/dL) unconjugated, albumin level was 4.2 g/L, globulin level was 2.8 g/L, alanine aminotransferase level was 2800 U/L, aspartate aminotransferase level was 2230 U/L, alkaline phosphatase level was 260 U/L, and prothrombin time was 12.9 seconds. Results of tests for hepatitis A antibody, hepatitis B markers, cytomegalovirus antibody, and mononucleosis were negative. Circulating hepatitis C virus and hepatitis E virus were undetectable by polymerase chain reaction. Antibodies to nuclei, smooth muscle, soluble liver antigen, and liver kidney microsomes-1 were not detected, but atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA) were present at a titer of 1:160. Liver biopsy showed degeneration and necrosis of hepatocytes, portal and periportal lymphocytic infiltration, and focal bridging fibrosis without regenerating nodules. Prednisone therapy resulted in a prompt diminution of jaundice, symptoms, and aminotransferase levels. After 3 weeks of therapy, pANCA were present at a titer of 1:640, antimyelperoxidase antibody was not present, antibodies to nuclei were detected at a titer of 1:640, and smooth-muscle antibodies were detected at a titer of 1:80.

The patient had acute onset of type 1 autoimmune hepatitis that was initially characterized by the isolated autoantibody pANCA. Although pANCA has long been known to characterize primary sclerosing cholangitis and nonspecific ulcerative colitis, the realization that it is common in type 1 autoimmune hepatitis is more recent (1–5). The labeling patterns of atypical pANCA (also referred to as xANCA), which have been observed by using immunofluorescence techniques, suggest multiple antigens. Candidates include lactoferrin, cathepsin G, bactericidal-permeability-increasing protein, β-glucuronidase, and nuclear lamins (1, 4, 5). This report demonstrates that in patients with acute-onset type 1 autoimmune hepatitis, atypical pANCA may be the only antibody detectable at presentation; the pattern of autoantibodies, however, may vary with time.

Edward L. Krawitt, MD
University of Vermont College of Medicine
Burlington, VT 05405-0068

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Retroperitoneal Hematoma and Enoxaparin

To the Editor: Spontaneous retroperitoneal hematoma associated with the use of enoxaparin is not widely reported. A MEDLINE search of the literature from 1966 to April 1999 revealed no cases associated with the current recommended therapeutic dose of 1 mg/kg of body weight every 12 hours (1). We describe a patient who developed a fatal hematoma after use of enoxaparin for acute deep venous thrombosis.

A 69-year-old man was transferred to our facility for management of a urinary tract infection. His medical history included ischemic cardiomyopathy, chronic renal insufficiency, localized prostate cancer, and chronic anemia. He had no history of coagulopathy, renal tumors, liver disease, or abdominal aortic aneurysm. He took no antiplatelet agents or anticoagulant agents. No adverse drug reactions were reported. He had no family history of coagulopathy and reported no long-term alcohol use. The initial physical examination revealed no peritoneal signs, abdominal bruising, or scrotal hematoma. Laboratory data

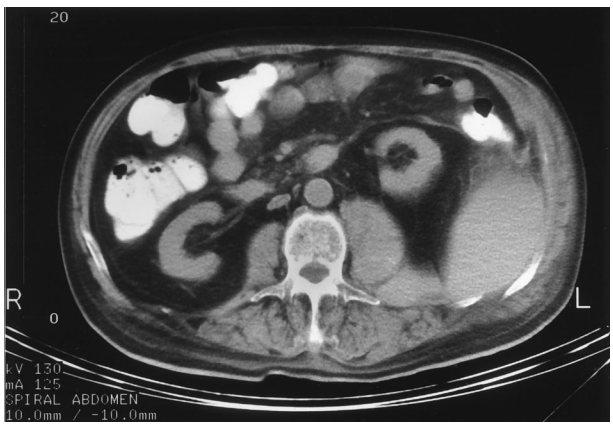

Figure. Computed tomographic scan of the abdomen. Retroperitoneal hematoma measuring 7.5 cm × 15 cm, displacing the left kidney and the descending colon anteriorly and involving the left iliopsoas muscle.

showed a hemoglobin level of 9.3 g/dL, a normal platelet count, and a creatinine concentration of 300.6 μmol/L (3.4 mg/dL).

Vancomycin and piperacillin–tazobactam therapies were continued for the infection. Aspirin treatment was started for a complicating non–Q-wave myocardial infarction. The patient developed acute deep venous thrombosis of the right common femoral vein, which was diagnosed by lower-extremity Doppler examination. The patient began receiving 80 mg of enoxaparin subcutaneously every 12 hours. Four days later, he became hypotensive. Abdominal examination revealed new periumbilical bruising, and the patient's hemoglobin level decreased to 6.9 g/dL. Abdominal computed tomography (**Figure** on page 796) showed a left retroperitoneal hematoma measuring 7.5 × 15 cm. No aortic aneurysm was noted. The patient died despite supportive care.

Enoxaparin has advantages over unfractionated heparin (2, 3), but clinicians must be wary of potential complications. Reports of associated spinal hematoma have already been noted, and synergism between aspirin and enoxaparin has been described (3, 4). Finally, retroperitoneal hematoma has been reported with dalteparin, another type of low-molecular-weight heparin (5).

Jean-Paul Montoya, MD
Texas A&M University Health Science Center
College of Medicine
Temple, TX 76508

Nagaprasadrao Pokala, MD
Stephen L. Melde, MD
Central Texas Veterans Healthcare System
Temple, TX 76504

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Long QT Syndrome and Torsade de Pointes in a Patient Receiving Fluconazole

To the Editor: A 59-year-old woman with liver cirrhosis and peritonitis was admitted to our hospital. *Candida albicans* was detected in ascitic fluid, and intravenous therapy with fluconazole (400 to 800 mg/d for 5 weeks) was given, followed by intraperitoneal administration (150 mg/d). One day after the second intraperitoneal administration, palpitations, polymorphic ventricular premature complexes (VPC), and syncope occurred. Results of cardiovascular examination were normal. In contrast to a normal electrocardiogram at admission, electrocardiography now showed polymorphic VPC, T-wave inversions, alternating T-wave amplitudes, and a prolonged time-corrected QT interval (QTc) of 606 ms. Findings on echocardiography and chest radiography were normal. Thyroid hormone and serum electrolyte levels were within normal ranges, especially levels of potassium, magnesium, and free calcium. No signs of myocardial damage were detected; the troponin T level was normal. Despite these findings, a torsade de pointes tachycardia occurred, requiring cardiopulmonary resuscitation. A fluconazole plasma level of 216 μg/mL was found. Usually, therapeutic plasma levels of 18 to 28 μg/mL are seen with administration of 400 to 800 mg of fluconazole per day (1). Fluconazole therapy was discontinued. Arrhythmia ceased within 3 days. The QT interval normalized within the next 3 weeks (QTc, 423 ms), and morphologic characteristics on electrocardiography were normal.

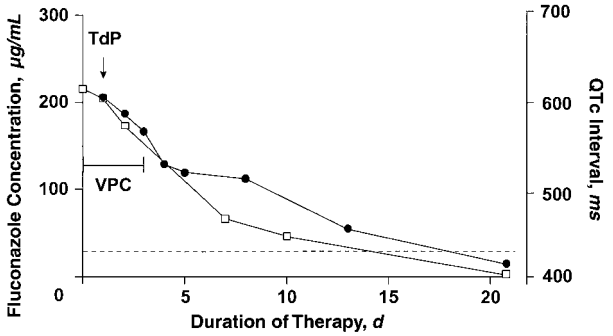

Figure. Plasma concentrations of fluconazole (*squares*) and corrected QT interval (*QTc*) (*circles*) during 21 days after the first manifestation of arrhythmia. The dotted line indicates the expected fluconazole concentration in persons receiving 800 mg/d. VPC = ventricular premature complexes; TdP = torsade de pointes.

Acquired QT prolongations are mainly caused by drugs (2). Triazole antimycotic agents may lead to QT prolongation by inhibition of the hepatic metabolism of other QT-prolonging drugs (3). Direct effects of fluconazole on QT interval have not yet been shown. In our patient, QT prolongation was probably directly caused by fluconazole because the patient was receiving no concomitant drugs with known QT-prolonging potential. Fluconazole plasma levels were dramatically elevated when arrhythmia occurred and were strongly correlated with the extent of QT prolongation over time (**Figure** on this page). Most important, arrhythmia disappeared and QTc decreased when fluconazole therapy was discontinued but concomitant medication remained unchanged. No other causes of QT prolongation, such as electrolyte disturbances or neurologic, endocrine, or cardiac disorders, were present.

We report the direct QT-prolonging potential of fluconazole. Concomitant medication with other QT-prolonging drugs and electrolyte disturbances should be avoided. The fluconazole dose should be substantially reduced in patients with renal impairment. Intraperitoneal application may be hazardous in persons with an inflamed peritoneum caused by unforeseeable alterations of drug resorption (4).

Sven Wassmann, MD
Georg Nickenig, MD
Michael Böhm, MD
University of Cologne
50924 Cologne, Germany

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Treatment of Parathyroid Cysts with Fine-Needle Aspiration

To the Editor: Parathyroid cysts are a rare cause of cervical or mediastinal masses, with only about 230 cases reported to date (1). We report on 13 patients whose parathyroid cysts were diagnosed and treated by percutaneous aspiration of the cystic fluid. The 13 patients (4 men and 9 women) ranged in age from 12 to 84 years and were taken from a consecutive series of 2050 patients undergoing thyroid fine-needle aspiration. Twelve patients were treated by simple aspiration, in which the cystic fluid

was drained as completely as possible. After the first aspiration, the patients were asked to return in 1 month. If the fluid had reaccumulated, a second aspiration was performed; otherwise, the patients were instructed to return semiannually. One patient lived in too remote an area to return conveniently for follow-up. She requested a condensed treatment course and underwent sclerotherapy with tetracycline hydrochloride.

The quantity of aspirated fluid ranged from 2 to 80 mL (mean ± SD, 29.2 ± 28.1 mL). The parathyroid hormone concentrations were extremely high in five samples (>1200 ng/dL) and were elevated in eight (range, 49.3 to 498.7 ng/dL). Parathyroid cysts resolved after only one aspiration in 10 patients and after a second aspiration in 2 patients. One patient had three aspirations combined with sclerotherapy. During 1 to 8 years of follow-up (mean ± SD, 5.2 ± 3.7 years), none of the 13 patients experienced recurrence.

Open surgery was the exclusive treatment for parathyroid cysts until 1978, when Clark (2) cured a nonfunctioning parathyroid cysts by percutaneous aspiration. In the same year, Ginsberg and coworkers (3) also cured two patients by one simple aspiration. However, in a 1985 review of seven patients, Pacini and colleagues (4) reported mixed results: One aspiration was successful in five patients, but cysts recurred in two patients who then required surgery. Kodama and coworkers (5) had even more disappointing results; of nine parathyroid cysts, six failed to resolve. This review of the literature shows ongoing controversy about use of fine-needle aspiration.

In our experience with 13 patients, fine-needle aspiration was safe and effective, and we propose that it be considered as the first-line treatment for parathyroid cysts. If cysts recur after two or more aspirations, sclerotherapy with tetracycline solution or ethanol—a procedure that is simple and less expensive than surgery—can be used in combination.

Bingyin Shi, MD
Hui Guo, MB
Nan Tang, MD
Xi'an Medical University
Xi'an 710061, China

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"Catastrophic" Diagnosis of the Antiphospholipid Syndrome

To the Editor: A 41-year-old male smoker developed blurred vision, right arm weakness, and aphasia. Examination showed no heart murmur and multiple subungual hemorrhages. Lupus anticoagulant was detected, with low levels of anticardiolipin and antinuclear antibodies and no cryoglobulin, double-stranded DNA, or extracted nuclear antigen antibodies. Magnetic resonance imaging showed a left parietal infarction. Echocardiography revealed mitral vegetations (**Figure**). Funduscopy showed retinal vein occlusion. Blood cultures remained negative.

The patient was referred for the antiphospholipid syndrome. Atypical findings—dorsalgia, cervical lymphadenopathy, fever, and weight loss—led to further work-up. Bronchoscopy showed a tracheal lesion that was negative on biopsy; node smears were also negative. Magnetic resonance imaging demonstrated a T3 image, which was diagnosed on biopsy as mucosecreting carcinoma metastasis. Mechanical hemolysis (regenerative anemia with schistocytes, negative results on the Coombs test, and low haptoglobin level) and disseminated intravascular coagulation were evident. Serum CA15.3 level was extremely elevated. Lupus anticoagulant and high levels of IgG anticardiolipin antibodies were present, without antibodies to β_2-glycoprotein I. The patient died after developing left hemiparesis and respiratory distress. Autopsy confirmed carcinoma of unknown origin with lung miliary, thrombotic nonbacterial mitral vegetations, and renal and cerebral infarctions.

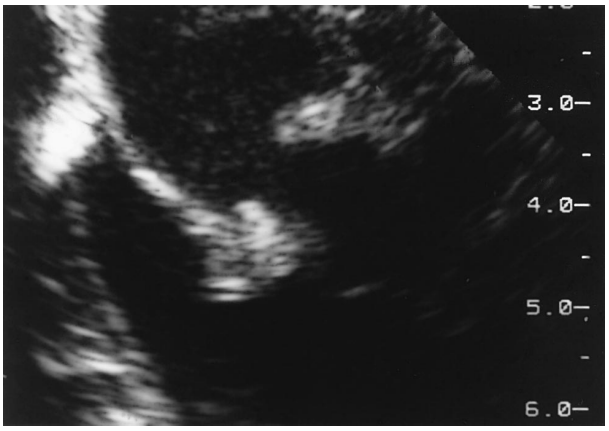

Figure 2. Transesophageal echocardiogram. Large nodular vegetations are present on free margins of both mitral leaflets.

Thrombosis and the presence of lupus anticoagulant or anticardiolipin antibodies define the antiphospholipid syndrome. Its cardiac manifestations include valve thickening or vegetations, which sometimes cause cerebral embolism (1). Catastrophic cases of the antiphospholipid syndrome present as multiple simultaneous occlusions (2). Our patient fulfilled all of these criteria (2) but had paraneoplastic endocarditis: Splinter hemorrhages have not been reported to date in patients with paraneoplastic marantic endocarditis. The risk for overlooking cancer in patients with recurrent thrombophlebitis and cancer-related antiphospholipid syndrome has been noted (3, 4), but little is known about arterial manifestations caused by left-sided thrombotic paraneoplastic endocarditis mimicking the antiphospholipid syndrome. Bessis and colleagues (5) reported a patient presenting with stroke, thrombophlebitis, mitral vegetation, lupus anticoagulant, and antiphosphatidylinositol antibodies who had metastatic lung adenocarcinoma. Ruffatti and coworkers (4) described a woman with thrombophlebitis, pulmonary embolism, tricuspid vegetation, lupus anticoagulant, and IgM anticardiolipin antibodies who had ovarian adenocarcinoma.

Marantic endocarditis may masquerade as catastrophic cases of the antiphospholipid syndrome (2). Clinicians must search for occult cancer in patients with a recent possible diagnosis of the antiphospholipid syndrome featuring "atypical" associated manifestations (3).

Jean-Charles Piette, MD
Zahir Amoura, MD
Hôpital Pitié-Salpêtrière
75013 Paris, France

Anne Foucher-Lavergne, MD
Hôpital Lariboisière
75010 Paris, France

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Posterior Pituitary Sigma Receptors and Drug-Induced Syndrome of Inappropriate Antidiuretic Hormone Release

To the Editor: Long-term administration of neuroleptic agents has occasionally been associated with the development of a drug-induced syndrome of inappropriate antidiuretic hormone release (SIADH). As early as two decades ago, investigators recognized that haloperidol could impair a patient's ability to excrete a free water load (1). In the absence of other abnormalities in endocrine function, long-term administration of haloperidol was observed to induce a state of hyponatremia and serum hypoosmolality. This phenomenon was reversed after discontinuation of therapy with the drug.

Although haloperidol is known to function clinically as a pharmacologic antagonist at mesolimbic D2 dopamine receptors, it has also recently been shown to bind with high affinity to neuronal sigma receptors (2, 3). Sigma receptors, first described in the 1970s, were initially thought to represent a novel subtype of opioid receptors (2). However, subsequent pharmacologic analysis has shown that the sigma receptor represents a discrete molecular entity. A human sigma receptor complementary DNA has recently been cloned, and its predicted amino-acid sequence codes for a protein with an approximate molecular mass of 26 kd (4). The normal physiologic function of this protein has yet to be determined.

Researchers at our laboratory have recently demonstrated that sigma-receptor ligands, including haloperidol and chlorpromazine, can inhibit potassium-channel function in the posterior pituitary (5). Furthermore, photoaffinity labeling and electrophoretic analysis have shown that these ligands exert their effect by binding to a neurohypophysial sigma receptor with a molecular mass of 26 kd. Because this sigma receptor–mediated inhibition of neurohypophysial potassium current would be expected to increase the release of neurohypophysial hormones, our results provide a mechanistic explanation for the drug-induced SIADH associated with long-term use of haloperidol or chlorpromazine. Of interest, clozapine (a newer, atypical antipsychotic agent) has no measurable effect on potassium current in the posterior pituitary (5). To date, there have been no reports of SIADH associated with long-term use of clozapine.

Russell A. Wilke, MD, PhD
University of Wisconsin Hospital and Clinics
Madison, WI 53706

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