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INSIDE

Inflammation and Lung Cancer Survival

ABSTRACT & COMMENTARY

Synopsis: *The Glasgow Prognostic Score (GPS) is an easily derived measure of underlying inflammatory processes. In this series of 101 patients with newly diagnosed advanced non-small cell lung carcinoma, it proved superior to the ECOG Performance Scale in predicting survival. After initial treatment, however, the prognostic value fell, but this may have been the result of fewer evaluable patients at the latter time points.*

Source: Forrest LM, et al. *Br J Cancer*. 2005;92:1834-1836.

Non-small cell lung cancer (NSCLC) remains the most common cause of cancer related death in the United States. Progression of the disease is characterized by nutritional and functional decline, and some have conjectured this relates to disease-associated systemic inflammation.[1,2] The Glasgow Performance Score (GPS) is an inflammation-based scale which, when calculated at initial diagnosis, has been shown to correlate with survival for patients with NSCLC.[1] To derive the GPS score, patients with both an elevated C-reactive protein ([CRP] > 10 mg/L) and hypoalbuminemia (< 35 g/L) are allocated a score of 2. Patients in whom only one of the biochemical abnormalities is present are scored 1, and those in whom neither is present, 0.[3] The current investigation was undertaken to determine if the GPS would be a useful prognostic determinant at later points in the course of patients with this disease.

For this, 101 patients with inoperable NSCLC were scored at diagnosis and at 3 and 6 months after diagnosis for both GPS and performance status (ECOG). Approximately half of the patients had stage IV disease. At diagnosis, 68% had elevated CRP and 10% had low serum albumin. The majority were ECOG PS 0 or 1. During follow-up, 29 of 42 receiving 'active' treatment and 55 of 59 receiving 'palliative' treatment died. Only 38 were available for follow-up assessment.

At diagnosis (stratified for treatment, active vs palliative), only the GPS (hazard ratio, 2.32; 95% CI, 1.52-3.54; $P < 0.001$) was signifi-

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cantly associated with survival. At the follow-up assessment (3-6 months), there was a reduction in ECOG-PS ($P < 0.01$) and GPS ($P < 0.10$), but neither were significantly associated with subsequent survival ($P = 0.08$ for ECOG-PS; $P = 0.139$ for GPS).

COMMENT BY WILLIAM B. ERSHLER, MD

This brief report is of interest because 2 commonly obtained laboratory measures, when used in concert offer prognostic information beyond the more subjective performance status that most oncologists appreciate. Incorporation of this simple assessment may prove valuable in both research and clinical deliberations. The fact that neither measure (ECOG-PS or GPS) offered prognostic significance during or after treatment in this study probably relates more to the diminished number of evaluable patients at the latter time points. Indeed, it appears by the reported *P* values that trends were there and with a larger series, these too, might reach significance. However, at the latter points, impairment in performance status or GPS may in some way be confounded by treatment effects and thereby less likely to completely reflect perturbations produced by the underlying disease.

There is a currently developing appreciation of the importance of inflammatory processes at the root of heretofore considered unrelated chronic illnesses including atherosclerosis, diabetes, arthritis, dementia, and cancer. It may turn out that the GPS is of equivalent value for these other conditions as well.

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Multicenter Comparison of Laparoscopic vs Conventional Surgery for Colorectal Cancer

ABSTRACT & COMMENTARY

Synopsis: *Laparoscopic surgery is rapidly becoming more commonly used for colorectal cancer resection. The current study reports the short-term findings of a relatively large, randomly assigned comparison of laparoscopic surgery vs standard open procedure for patients with newly diagnosed colon or rectal cancer. With the exception of laparoscopic anterior resection for rectal cancer, short term markers of success were comparable. This data set, as it matures, will provide additional information that will help define the role for laparoscopically assisted surgical procedures for this disease.*

Source: Guillou PJ, et al. *Lancet*. 2005;365:1718-1726.

Laparoscopic-assisted surgery offers a theoretical advantage of more rapid recovery, fewer complications, and shorter duration of hospital stay. Accordingly, there has been an increased adaptation of this approach for a wide variety of procedures, including the potentially curative resection of colon or rectal carcinoma. Yet, there remain little data from large-scale prospective randomized trials that would support such an approach. The current report is that of short-term results from one such trial.

Guillou and colleagues report from the UK Medical Research Council (MRC) trial of conventional vs laparoscopic-assisted surgery in colorectal cancer (CLASICC) is a randomized, controlled study undertaken by surgeons at 27 UK centers.

Eligible patients were candidates for hemicolectomy (right or left), sigmoid colectomy, anterior resection, or abdominoperitoneal resection for newly discovered colon cancer. Patients were excluded if their carcinoma was in the transverse colon, if they had bowel obstruction, synchronous carcinomas, or pulmonary or cardiac disease for which pneumoperitoneum or prolonged anesthesia would introduce unacceptable additional operative risks. Using a 2:1 randomization scheme, patients were allocated to receive laparoscopic-assisted (n = 526) or open surgery (n = 268). Primary short-term end points were positivity rates of circumferential and longitudinal resection margins, proportion of Dukes' C2 tumors, and in-hospital mortality. Analysis was by intention to treat.

The treatment groups were well balanced and the proportion of patients with Dukes C2 tumors was nearly identical (7% open, 6% laparoscopic). Similarly, in-hospital mortality was not different (5% vs 4%) and with the exception of patients undergoing laparoscopic anterior resection for rectal cancer, rates of positive resection margins were similar between treatment groups. For rectal cancer in general, positive margins were identified in 14% with open surgery and 16% with laparoscopically assisted surgery. However, for those undergoing anterior resection laparoscopically, margin positivity was greater (12% vs 6%; a trend, but not statistically significant) (95% confidence interval, -2.1 to 14.4%; $P = 0.019$).

In those assigned to laparoscopic surgery, 29% required intraoperative conversion to an open procedure. For the purposes of analysis, these individuals were included in the laparoscopic treatment arm (intention to treat analysis). However, they were also examined separately. Individuals who had converted procedures had a higher percentage of Dukes C2 tumors ($P = 0.19$, NS). The most common causes for conversion were excessive tumor fixity (ie, difficulty in removal), uncertainty of tumor clearance, and obesity. In addition, for rectal cancers specifically, some cases were converted because of anatomic uncertainty and others for inaccessibility of tumor.

In summary, Guillou et al concluded that laparoscopically assisted surgery for cancer of the colon is as safe and effective as open surgery in the short term, and likely in the long term as well. However, impaired short-term outcomes after laparoscopic-assisted anterior resection for cancer of the rectum raised enough concern that Guillou et al felt that routine use was not warranted at present.

COMMENT BY WILLIAM B. ERSHLER, MD

Randomized, prospective studies of laparoscopic surgery for colorectal carcinoma have been limited in number and scope. That stated, the current report, which is an early analysis of a series that will generate important long-term results in years to come, is large and well designed. Furthermore, the inclusion of patients with rectal cancer and the suggestion that those treated by laparoscopic anterior resection had a worrisome trend for increased unclear margins is an important finding, even at this preliminary stage.

The data thus far for colon cancers are quite similar to that for smaller series, for which survival data have been published. For example, Leung and colleagues just last year[1] reported experience from their Hong Kong centers on 403 colon cancer patients who were randomly assigned to either laparoscopic procedure or open surgery. The 5-year survival rate for the laparoscopic group was slightly greater than that of the open resection group (76.1% vs 72.9%). However, patients in the laparoscopic resection group had a slightly lower probability of being disease free at 5 years than those in the open resection group (75.3% vs 78.3%), but neither of these findings were significant. The postoperative recovery for the laparoscopic group was significantly better, but the operative time for the laparoscopic procedure was significantly longer and the direct cost was greater. The overall morbidity and operative mortality was the same between the 2 groups. Thus, the UK experience is quite similar and Guillou et al's prediction—that the lack of difference observed in early markers (such as tumor margins) will ultimately reflect comparable cure rates—is likely to be true. Nonetheless, although the numbers are somewhat larger, the UK trial itself will be inadequate to definitively declare equivalence.

Thus, the issue will ultimately come down to weighing the benefits of laparoscopic surgery against the risks and added costs, which may include longer periods of anesthesia and the additional training required to become procedurally competent. Regarding the benefits, short-term complications and quality of life may actually be comparable, as demonstrated in the UK trial. So, the real difference may be that of cost reduction as a result of reduced hospital stay. To this reviewer, it seems that this technical advance may ultimately be considered modest at best. ■

Reference

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Proteomic Profiling in Ovarian Cancer: Is it Plausible?

ABSTRACT & COMMENTARY

Synopsis: *The reproducibility of the proteomic profiling approach has yet to be established.*

Source: Baggerly KA, et al. *J Natl Cancer Inst*. 2005;97: 307-309.

Reproducibility of complex proteomic signatures in detecting early stage ovarian cancer has proven to be a significant challenge in the field of biomarker discovery. Although early reports of proteomic profiling demonstrated near 100% sensitivity and specificity in discriminating ovarian cancer from non-cancer, the ability to reproduce these results across datasets has been difficult. Baggerly and colleagues examined 2 proteomic spectral datasets available in the public domain with the intent of testing the published classification method and assessing reproducibility. They then calculated the probability that classification could occur by chance alone. Using statistical methodology similar to the original reports then followed by random allocation of spectral clusters, Baggerly et al report that the predictive spectral peaks were less accurate (less than 80%) than originally reported. Applying a separate methodology (jack-knife approach) to test the original peaks to a second dataset produced high accuracy (98.4%). However, this level of accuracy was met or exceeded in 6% of the simulations using completely random values. On the basis of these 2 findings, Baggerly et al concluded that proteomic signature profiling to accurately and reproducibly discriminate cancer from non-cancer was not plausible and may be the effect of procedural bias.

COMMENT BY ROBERT L. COLEMAN, MD

News of accurate discrimination of cancer patients from unaffected patients via evaluation of blood samples was a welcomed and widely publicized advance in the field of ovarian cancer screening research. Although difficult to understand, the technology of developing and interpreting proteomic signatures from banked blood of both cancer patients, patients with non-cancerous lesions, and normal controls, appeared to offer renewed hope in the ability to accurately classify patients with disease, particularly those with early stage disease, where survival is the best. While the data being produced were patterns (spectral peaks) recognizable only by sophisticated statistical algorithms sensitivity, specificity and accuracy were very high and far better than our best (and current) biomarker methodology. However, almost as soon as the data were reported, news of the inability to accurately reproduce the data permeated the clinical community who were already baited with the promise of a commercial product awaiting approval. The current report, on the surface, seems to dampen that enthusiasm even more where the results of 2 independent data sets were found to not be reproducible and could be explained by chance—that is by overfitting. Overfitting errors are encountered when a multivariate model is used to fit a very large number of possible predictors. Indeed, Baggerly et al demonstrated that simply choosing random spectral peak values for a prediction model met or exceeding the predictive accuracy of the historical model in 6% of their samplings. This would imply that the plausibility for prediction based on the public domain datasets was low and confounded.

The Baggerly article is followed by 2 commentaries in the *Journal of the National Cancer Institute* that help to put this apparent conundrum into perspective.[1] We find from the original authors of one of the sentinel articles that the datasets placed into the public domain was generated from experimental settings where one or more parameters were purposefully altered to study the effects on output spectra. In this situation, the datasets would likely not be reproducible as the baseline between sets is intentionally and artificially adjusted. In addition, it was raised that issues of reproducibility are premature as the technology is a moving target and continuously updated. However, as is discussed in the second commentary, reproducibility is the lifeblood of moving this complex promising field (termed "-omics") forward. It is further complicated by the dichotomy of discovery; on the one hand, you have a test based on pattern recognition alone, where the results are based on unknown and undescribed proteins, and on the other, you have biomarkers development, which would take on the tedious process of describing these proteins, showing their relevance (biological impact) to ovarian cancer and then develop a measurable antibody in the patient's sera. Calls for a new trial have been made, where reproducibility is the mission, in a single data set with careful attention to statistical methodology.[2,3]

What is clear from the 10 pages of commentary that accompanies the 3-page brief communication is that this field holds tremendous promise in promoting our ability to identify at-risk patients, but must be embarked upon carefully. In addition, free interchange and discussion through publicly disseminated data will help perfect this important task. ■

Dr. Coleman is Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston.

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Taking Time to Start XRT for Localized Prostate Cancer: It's Not for Everyone

ABSTRACT & COMMENTARY

Synopsis: *Delays in starting radiation therapy for high-risk localized prostate cancer were shown in this retrospective review to be associated with a greater risk for disease relapse, as witnessed by PSA recurrence. For patients with low-risk disease, however, comparable delays were not associated with greater risk for relapse.*

Source: Nguyen PL, et al. *Cancer*. 2005;103:2053-2059.

A DELAY OF 3 MONTHS BETWEEN DIAGNOSIS OF CLINically localized prostate carcinoma and initiation of treatment is not uncommon for patients who ultimately choose radiation therapy. This interval is significantly longer than delays commonly observed for other cancers such as head and neck, cervical, lung or breast carcinoma. There are probably several reasons for this including the time for appropriate consultations, obtaining second opinions, etc, and possibly a complacency based upon a notion that prostate cancers are indolent and unlikely to progress rapidly.

Nguyen and colleagues performed a retrospective analysis to determine whether a delay in initiating external beam radiation therapy following diagnosis could impact prostate-specific antigen (PSA) outcome for patients with localized prostate cancer. For this, the data from 460 patients between 1992 and 2001 who received 3D conformal RT to a median dose of 70.4 Gy for T1c or T2 prostate cancers, without evidence of spread beyond the capsule were analyzed. The primary end point was PSA failure (American Society for Therapeutic Radiology and Oncology definition) and delay was measured as the time interval between diagnosis and initiation of treatment.[1] Risk groups were defined by PSA at baseline, clinical T category, Gleason score and the percentage of biopsy cores positive for tumor.

Of the 460 patients, 220 were considered at low risk, and for them treatment delay was not a significant predictor of time to PSA failure ($P = 0.31$). However, in contrast, for those considered at high risk, treatment delay was a significant predictor of time to PSA failure (adjusted hazard ratio = 1.08; 95% CI, 1.01-1.16 per month; $P = 0.029$). The patients with high-risk disease had 5-year estimates of PSA failure-free survival of 55% if their treatment delay was greater than 2.5 months compared to 39% if the delay was less than 2.5 months ($P = 0.014$).

COMMENT BY WILLIAM B. ERSHLER, MD

Thus, for patients with high risk but localized prostate cancer, about half of treated patients of the current trial had a significant decline in disease-free survival. This, of course, would makes intrinsic sense to tumor biologists familiar with the relentless nature of cancer cells to grow and spread, particularly for those with biochemical or histological features of aggressive disease. Nonetheless, there is a commonly observed complacency in getting started with initial treatment for prostate cancer. Some of this is due to the availability of diverse treatments within radiation oncology (external beam, brachytherapy, etc), and, of course, surgery. It is not uncommon for patients to seek opinions from one or more surgeons as well as radiation oncologists, and then to deliberate for considerable time before making a treatment decision. Indeed, in this series, the median time from diagnosis to treatment was 2.5 months. It is unlikely that this is unique to the communities represented in this report. Patients who elect surgery are also likely to be treated after a delay. In this regard, 2 recent reports[2,3] have shown that a delay of 3 months before prostatectomy was also associated with less favorable outcomes in patients with markers of high-risk (high baseline PSA or poorly differentiated) tumors.

Currently, neoadjuvant hormonal ablation is becoming more commonly used. For those with markers of high-risk disease and who anticipate a delay in definitive initial therapy, it might be reasonable to consider this approach. However, the use of such an approach in diminishing relapse rates in the context of initial treatment delays has not been established. Yet, if current trials of neoadjuvant hormonal therapy prove beneficial to radiation or surgery alone, it would seem a logical extension would be to so treat high-risk patients with localized disease while they are considering treatment options. ■

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Special Feature

Systematic Lymphadenectomy in Ovarian Cancer Surgery: Now We Know!

By Robert L. Coleman, MD

The well-known mantra of primary ovarian cancer management is surgery. The procedure has modified little in the last 30 years as the goal in advanced cases has been cytoreduction and, in seemingly early cases, it has been accurate staging. Although, heretofore unstudied in a randomized fashion, surgery has decisive merit, reflected in better long-term survival for those patients with metastases rendered disease-free, and in increased precision of therapy through the avoidance of over- or under-treatment in limited-stage patients.[1,2] In the latter scenario, systematic evaluation of all sites of spread is critical to accurate representation of the disease process. It is now well described that as many as 30% of patients with limited-stage disease will be upstaged on the basis of systematic biopsies, and under-sampling leads to higher misclassification—an event usually associated with early recurrence.

One target area of continued interest has been the retroperitoneum. Clinicopathologic studies have reported that approximately 10-15% of grossly non-metastatic ovarian cancer patients and 40-70% of metastatic patients will have retroperitoneal metastases, particularly in the paraortic regions. Their presence has been associated with poor clinical outcome. Thus, in 1988, FIGO amended the staging classification of ovarian cancer to include a subclassification for retroperitoneal metastases. In addition, many investigators and clinicians have described the retroperitoneum as a *safe-haven* of disease being less sensitive to systemic chemotherapy. What has been debated for more than 2 decades is whether systematic lymphadenectomy should accompany a debulking effort, particularly for those in whom complete or near complete intraperitoneal resection is feasible. Proponents, supported by retrospective clinical data, state that retroperitoneal resection will allow truly complete cytoreduction and removal of treatment sanctuary sites leading to improved survival. Further, they contend that basing a decision for resection on intraoperative nodal morphology is hazardous and unreliable, potentially overlooking more than half of the metastatic cases, even those greater than 1 cm![3,4] Opponents counter, stating that the procedure has attendant morbidity, adds unnecessary time and cost to the already long operation, and adds little value in a patient with grossly apparent metastatic intraperitoneal disease. Further, they take issue with the contention that the nodal reservoirs are chemoresistant, citing many trials of patients with metastatic retroperitoneal disease that respond to chemotherapy and noting, retroperitoneal-only recurrence is a rare phenomenon in this diseaese.[5]

Settling the score and highlighting the scientific prowess of dedicated investigators comes the recently published randomized clinical trial from Benedetti-Panici and colleagues evaluating the performance of systematic lymphadenectomy in otherwise, optimally cytoreduced stage III and IV ovarian cancer.[6] Even if the subject of this debate holds little interest to the reader, one must congratulate these clinicians on completing an extremely difficult, randomized, proof-of-principle study among surgeons regarding—surgery! If nothing else, it is proof that the often used "crutch" debate position, ". . . this [insert unique clinical situation] could really only be solved by a randomized clinical trial—which can't be done . . ." can indeed be overcome. In the study, 452 patients were enrolled from 13 centers located in 5 countries. Less than 6% were excluded after randomization and the cohorts were well balanced for known prognostic factors such as stage, grade, histology and tumor residual. Although eligible if defined by malignant pleural effusion, no stage IV patients were enrolled. Patients were allocated to retroperitoneal lymphadenectomy or simple biopsy intraoperatively after optimal intraperitoneal cytoreduction had been achieved. Optimal debulking was defined as less than or equal to 1 cm residual. The minimum requirements for systematic lymphadenectomy in this trial were impressive. Complete en bloc excision of all node-bearing tissue from the pelvic, common iliac, and paraortic regions was required. No less than 25 pelvic and 15 paraortic nodes were considered an appropriate dissection in the experimental cohort. Those patients randomized to simple biopsy were to have inspection of the retroperitoneum with excision of any grossly evident metastasic nodes. In all, just 8% of those randomized to no lymphadenectomy had too many nodes resected and just 13% of lymphadenectomy patients had too few (less than 25 pelvic

or 15 paraortic nodes) resected. All, however, were included in the intent-to-treat analysis. Following surgery, all patients received platinum-based chemotherapy, however, the specific regimen was not proscribed.

As anticipated, performance of the extended operation did increase operative time, blood loss, and transfusion, but hospital stay, while long in both cohorts, was equivalent. There were also more perioperative complications observed in the lymphadenectomy cohort, consisting of, predominately, lymphocysts and lymphedema. Little other complication data are described including their impact on quality of life. In terms of the primary end point and overall survival, no difference was observed (56.3 mos vs 62.1 mos; HR, 0.97; $P = 0.77$) between the 2 cohorts. Recurrence was observed in 69% of the control arm and 63% of the experimental arm. Time to recurrence, measured as progression-free survival, was statistically improved in the lymphadenectomy cohort. In this regard, there was a 24% reduction in the risk of progression for those patients undergoing systematic lymphadenectomy relative to biopsy alone ($P = 0.02$). The difference amounted to 5-7 months, depending on the statistical methodology used to describe this difference. Interestingly, the pattern of recurrence between the two groups was no different, with isolated retroperitoneal recurrence seen in just 2% of both cohorts. The finding of metastatic retroperitoneal disease overall was an adverse prognostic factor in this optimal cytoreduced population. However, whether lymphadenectomy offered any benefit among these patients was not directly analyzed and is still unknown. Multivariate analysis teased out only residual tumor as the independent prognostic variable to overall survival.

The trial is commendable on many levels already alluded to above and should serve as a reference point in addressing this issue for patients undergoing optimal cytoreduction. The results of this trial and the patterns of recurrence suggest that the retroperitoneum is probably not a major sanctuary for tumor growth and that intraoperative inspection may be sufficient for evaluation of metastatic disease. The appearance of a progression-free survival endpoint not reflected in a benefit to overall survival is unusual in primary therapy trials but not unheard of.[7] Such observations always evoke consideration of a detection bias, in which the observation under study (in this case, progression-free survival) is not equally probable between the two arms. In other words, could the performance of lymphadenectomy affect how recurrence is determined through imaging, biochemical marker evaluation or both? Another possibility is that modern chemotherapy given after recurrence could have made up any small change demonstrated in intermediate endpoints. While likely to be lost in the randomization process, such effects should be considered. For instance, nearly 85% of randomized patients came from one area. Practice patterns in this one site could have profound effects on the trial post-randomization. Nonetheless, the trial's conclusions are in line with their pre-trial expectations and reflect good data in a difficult to study arena. ■

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CME Questions

13. Delays in therapy of 2 ½ months or more in the initiation of external beam radiation therapy for localized prostate cancer was demonstrated by Nguyen and colleagues to be associated with:

a. higher rates of PSA failure in those considered at high risk based upon baseline PSA and histological features.
b. higher rates of PSA failure for all patients (i.e., for those at both low and high-risk).
c. higher rates of PSA failure in those with minimal disease compared to those with larger primary tumors.
d. no change in the rate of PSA failure.

14. From the UK experience, it is apparent that laparoscopically-assisted surgery is likely to result in comparable outcomes for each of the following procedures except:

a. Resection of left sided colon cancer
b. Resection of right sided colon cancer
c. Resection of rectal cancer by abdominoperinal approach
d. Resection of rectal cancer by anterior approach.

15. The Glasgow Prognostic Score (GPS) employs the following measures to provide prognostic information regarding clinical outcomes such as survival.

a. Lactate dehydrogenase (LDH) and beta-2 microglobulin
b. Serum albumin and c-reactive protein
c. Orbiting satellite and radar equipment
d. Hemoglobin concentration and serum brain natriuretic peptide (BNP)

Answers: 13 (a); 14 (d); 15 (b)

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Is Nesiritide Associated with a Higher Death Rate?

Nesiritide, Scios' intravenous recombinant form of human B-type naturetic peptide, has been widely used for the treatment of congestive heart failure in hospitalized patients. On Scios' website, nesiritide is touted as the "best-selling IV cardiovascular drug ever brought to market." All that may change with the publication of a new study that suggests that patients with acutely decompensated heart failure (ADHF) treated with nesiritide have a higher death rate at 30 days compared with patients who are not treated with the drug. The study was a pooled analysis of 12 randomized, controlled trials, of which 3 met all inclusion criteria. In those 3 trials, 485 patients with ADHF were randomized to nesiritide and 377 to control therapy which was noninotrope-based treatment. Thirty-day death rate was higher among the nesiritide group (7.2% vs 4.0% for placebo, 1.74 risk ratio; 95% CI [0.97-3.12]; *P* = .059). The authors conclude that therapy with nesiritide may be associated with increased risk of death after treatment for acutely decompensated heart failure, and suggest that an adequately powered, controlled trial should be undertaken (*JAMA*. 2005;293:1900-1905). This follows an earlier study that suggested nesiritide may worsen in renal function in patients with ADHF. In that study, which was also a pool analysis from 5 randomized studies, 1269 patients with ADHF were reviewed. Nesiritide was associated with a significantly increased risk of worsening renal function, compared with noninotrope control therapy (RR, 1.52; 95% CI, 1.16-2.0; *P* = .003) or any control therapy, including noninotrope and inotrope based therapies (RR, 1.54; 95% CI, 1.19-1.98 ; *P* = .001). Even low-dose nesiritide was found to worsen renal function. The authors conclude that nesiritide significantly increases the risk of worsening renal function in patients with ADHF, but suggests further investigation to determine the prognostic importance of this finding (*Circulation*. 2005;111:1487-1491).

Stopping Aspirin Before Surgery

A new study suggests that stopping aspirin 5 days prior to surgery is optimal. Researchers from Ireland recruited 51 volunteers who were randomly assigned to 3 groups: placebo, aspirin 75 mg per day, or aspirin 300 mg per day. Utilizing template bleeding times and specific platelet function testing, all bleeding times normalized within 96 hours and all platelet function test normalized within 144 hours after discontinuing aspirin. By day 6, there was no demonstrable hemostatic defect in any of the volunteers. There was also no difference between the 75 mg or 300 mg dose of aspirin. The authors conclude the data sup-

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ports withholding aspirin for 5 days with elective surgery been performed on the sixth day (*J Am Coll Surg*. 2005;200:564-573). This study is important because of recent data that cardiovascular events are much more likely to occur in patients who had recently withdrawn from aspirin—with the peak of events occurring at 10 days (*Pharmacology Watch*. March, 2005). Safely stopping aspirin for 5 days prior surgery, with reinstitution as soon as possible after surgery, makes good clinical sense.

The Sponge Returns

The Today Sponge contraceptive device is returning to the US market this summer. Last marketed more than 10 years ago, the sponge was removed from the market because of manufacturing problems. It is being brought back by Allendale pharmaceuticals, whose manufacturing facility met FDA standards. The sponge, which was made infamous by a memorable *Seinfeld* episode, is an over-the-counter, round, disposable, soft sponge that is impregnated with spermicide. It is inserted vaginally, and can be kept in place for 24 hours and for multiple sexual encounters. When it was taken off the market in 1994, the sponge was the most popular over-the-counter female contraceptive available, with 250 million of them sold in the 11 years it was available.

Preventing Metabolic Syndrome

Metformin and intensive lifestyle intervention both help prevent metabolic syndrome in patients who have impaired glucose intolerance. In a study derived from the Diabetes Prevention Program, 1711 patients with impaired glucose tolerance (defined by World Health Organization criteria plus fasting glucose level < 95) were evaluated. More than half the participants (53%) had metabolic syndrome at the baseline. In patients who did not have metabolic syndrome, metformin 850 mg twice daily or intensive lifestyle intervention designed to achieve and maintain 7% weight loss and 150 minutes of exercise per week were both effective in preventing metabolic syndrome. Lifestyle intervention was the more effective intervention with a 41% reduction in the incidence of metabolic syndrome ($P < .001$) while metformin reduced the incidence by 17% ($P = .03$) compared to placebo. Three-year cumulative incidences of metabolic syndrome were 51%, 45%, and 34% in the placebo, metformin, and lifestyle groups, respectively. The authors conclude that both lifestyle intervention and metformin are effective in reducing the development of metabolic syndrome in patients with glucose intolerance, although the impact of lifestyle intervention was more marked than that of metformin (*Ann Intern Med*. 2005;142:611-619).

FDA Actions

The FDA has approved exenatide for the treatment of type 2 diabetes in patients who have not responded to other treatments. The drug was derived from lizard saliva, and represents a new class of antidiabetic agents known as incretin mimetics—which mimic the effect of GLP-1, a naturally occurring incretin hormone found in human gut. Exanatide normalizes postprandial physiology by stimulating beta cells to secrete insulin in glucose dependent fashion. In alpha cells, the drug normalizes the pathologic hypersecretion of glucagon in a glucose dependent fashion. It also slows gastric emptying and improves satiety, all which serve to reduce postprandial hyperglycemia. There is some evidence that the drug may also attenuates weight gain seen with other hypoglycemic agents and may even be associated with weight loss. The drug will be marketed by Eli Lilly and Amylin Pharmaceuticals under the trade name Byetta.

Ropinirole (Requip) has been approved for the treatment of moderate-to-severe restless leg syndrome (RLS), the first US medication to be approved for this indication. The drug has been available for the treatment of Parkinson's disease since 1997. The approval was based on 3 randomized, double-blind, placebo-controlled trials in adults diagnosed with moderate to severe RLS. All 3 studies demonstrated a statistically significant improvement in the treatment group receiving ropinirole. Side effects include nausea, extreme drowsiness, and dizziness, and the drug will be labeled to warning about the possibility of falling asleep while engaged in activities of daily living including driving. GlaxoSmithKline is enthusiastic about the prospect of treating the estimated 1 out of 10 adults in this country with restless leg syndrome, the most common cause of insomnia. ■