

2. Nathan C, Xie Q-W. Nitric oxide synthases: roles, tolls, and controls. *Cell* 1994; 78:915–918.
3. Schmidt HHW, Walter U. NO at work. *Cell* 1994; 78:919–925.
4. Rodeberg DA, Chaet MS, Bass RC et al. Nitric oxide: an overview. *Am J Surg* 1995; 170:292–303.
5. Lorente L, Aller MA, Rodríguez-Fabián G. et al. Psychoneuro-immune-endocrine system behavior in mechanical trauma. *Psicothema* 1995; 7:619–625.
6. Davies MG. The vascular endothelium: a new horizon. *Ann Surg* 1993; 218:593–609.
7. Kam PCA, Govender G. Nitric oxide: basic science and clinical applications. *Anaesthesia* 1994; 49:515–521.

LAUREANO LORENTE  
MARÍA-ANGELES ALLER  
JORGE-LUIS ARIAS  
JAIME ARIAS  
Madrid, Spain

March 25, 1996

Dear Editor:

We thank Drs. L. Lorente, M. A. Aller, J. L. Arias, and J. Arias very much for their comments regarding the potential functional role of nitric oxide (NO) in traumatic injury. Although NO certainly has a role in all of the endothelial functions that they described, studies to date have not been able to fully evaluate the role of NO within the whole organism when subjected to an exogenous stimulus. In particular, the multiple cytokine and biochemical cascades associated with trauma and injury certainly are complex. Although NO may have a role, it is unknown in what circumstances the actions of nitric oxide are paramount. As a result, most studies of NO have relied upon *ex vivo/in vitro* models. In addition, gross ablation of systemic NO production has been used in whole animal studies in an attempt derive some meaningful data. It is our hope that continued research into this area will better clarify the role of NO as a systemic biochemical mediator in many physiologic states, including that of trauma.

PAUL C. KUO, M.D.  
Baltimore, Maryland

March 11, 1996

Dear Editor:

I read the article by Lo and others<sup>1</sup> with great enthusiasm and interest. I agree that laparoscopic cholecystectomy is the current “gold standard” for the treatment of gallstone disease. This is evident from the enormous amounts of literature published, although only few are randomized, controlled trials, attesting to definite efficacy of the procedure.<sup>2</sup> However, one real issue that continues to befall laparoscopic cholecystectomy and still is a matter of current rigorous debate is the question of safety, especially with regard to the risk of bile duct injury. It is well known that the risk of bile duct injury at least quadruples in laparoscopic cholecystectomy *versus* open cholecystectomy.<sup>3</sup> I commend the authors for their complete success in

avoiding any such injury in their series. Theoretically, there is increased risk of various complications in operating on acutely inflamed gallbladder, and this risk is accentuated when the operation is done laparoscopically. The economic principle of “risk taking” to reduce cost and “maximize profit” has been quite influential in decision making on costing of health services in general. One wonders whether this “principle” can be applied ethically to the individual patient when making decisions on treatment.

Despite the favorable results published by the authors, I believe that early laparoscopic cholecystectomy still is an experimental adventure that needs proper prospective, randomized, controlled trials to test the efficacy and safety of early *versus* late operations. The article by the authors essentially is a case series of their experience analyzed retrospectively. I am disturbed by the authors describing their study to be prospective at one point in the paper and retrospective elsewhere. With the recent emphasis on the clarity of study designs and statistical analyses used, this confusion is not acceptable in publishing good-quality articles. The authors expressed their continuous variables in terms of mean  $\pm$  standard deviation and compared these in-between groups by using the Mann-Whitney *U* test. I agree to the valid use of this analytical test because of the small number of subjects in each group, but being a nonparametric test, it is the medians that should be compared between the study groups rather than the means.

The number of subjects in both the early and delayed groups are comparable—*i.e.*, 25 and 27. Being a retrospective study, I find this comparability a sheer lucky convenience that does not come too often. I wonder what made the authors decide to perform early laparoscopic cholecystectomy within 5 days of clinical diagnosis compared with delayed operation? The authors also mentioned that all 27 patients who underwent early operations had histologic confirmation of acute cholecystitis. On retrospective review of these 27 patients, not all of them satisfied a clinical diagnosis of acute cholecystitis. There were only 19 patients with fever  $> 37.5$  C, 20 with leukocytes  $> 10 \times 10^9/L$ , 24 with edematous gallbladder, and 23 with ultrasonographic Murphy's signs. The number of patients who actually presented with upper abdominal pain with tenderness under the right costal margin were not actually stated in the paper. The authors mentioned that there were nine patients with “previous biliary symptoms.” It is important, in my opinion, to specify these symptoms and the substantiated reasons as to why these symptoms were labelled biliary. Painless dyspepsia currently is considered not to be peculiar to gallstone diseases alone.<sup>4</sup> From clinical experience, it is well known that sometimes it is very difficult to distinguish with confidence between the two clinical syndromes of “biliary colic” and “acute cholecystitis,” despite the hematologic and imaging studies. I wonder how the authors resolve this issue in their practice, especially in the context of this study. Pathologically, one can envision that the acutely inflamed gallbladder presenting as an acute abdomen can have a spectrum of disease processes, from the mild (chemical) cholecystitis, which may actually take place in “biliary colic” syndrome to the most severe gallbladder empyema, with all the systemic manifestations. This heterogeneity in pathologic processes is clinically important with regard to decision making of the appropriate therapy, especially the timing of surgical intervention. Any future study to establish

the role of early (acute) laparoscopic cholecystectomy in the treatment of acute cholecystitis should address this issue clearly.

## References

1. Lo C-M, Liu C-L, Lai ECS, et al. Early *versus* delayed laparoscopic cholecystectomy for treatment of acute cholecystitis. *Ann Surg* 1996; 223:37-42.
2. Grace PA, Bouchier-Hayes D. Laparoscopic cholecystectomy. In: Darzi A, Grace PA, Pitt HA, et al. *Techniques in the Management of Gallstone Disease*. 1st ed. Blackwell Science; 1995: 90-97.
3. Lee VS, Chari RS, Cucchiario G, et al. Complications of laparoscopic cholecystectomy. *Am J Surg* 1993; 165:527-532.
4. Rome Group for the Epidemiology and Prevention of Cholelithiasis (GREPCO). The epidemiology of gallstone disease in Rome, Italy: part I, prevalence data in men. *Hepatology* 1988; 8:904-906.

ABD. HAMID MAT SAIN, F.R.C.S.ED.  
Edinburgh, United Kingdom

April 10, 1996

Dear Editor:

We appreciate the thoughtfulness and interest shown by Dr. Sain toward our article.<sup>1</sup> There was no doubt that our study was retrospective and the limitation of such a study with regard to the recuperation period after surgery was clearly spelled out in the discussion part. We did, however, prospectively collect the data of all our laparoscopic cholecystectomies performed since March 1991 on a standard code sheet to form a computer database. This form of prospective data collection ensured more accurate and complete data recording for subsequent retrospective review. Although the data collection was prospective, the study was a retrospective one, and there should not be any confusion. The Mann-Whitney *U* test compares neither the means nor the medians of two groups, but the sum of the ranks of each group. However, we agree that the median (range) may be a better representation for small groups without normal distribution.

Like most centers performing laparoscopic cholecystectomy for acute cholecystitis, our approach has evolved over the years. In the early part of the study period, we regarded acute cholecystitis as a contraindication to the laparoscopic approach. With improvement in confidence and techniques, we performed laparoscopic cholecystectomy after the acute inflammation subsided with conservative treatment and more recently, early laparoscopic cholecystectomy was performed during the acute attack. We believe that when laparoscopic cholecystectomy is to be performed during the acute phase, the operation should be done soon after admission because delaying operation increases the technical difficulty.<sup>2</sup> For logistic reasons, such as arrangement of ultrasonography and operating sessions, we performed all early operations within 5 days of admission.

Our three diagnostic selection criteria were clearly stated in the article and *all* patients satisfied a clinical diagnosis of acute cholecystitis. All patients presented with acute upper abdominal pain with tenderness under the right costal margin. All patients had either fever greater than 37.5 C or leukocytosis, but not necessarily both. All patients had an ultrasonographic diagnosis of acute cholecystitis based on some, but not necessarily all, of the six signs. Thus, the absence of ultrasonographic Murphy's sign did not preclude a diagnosis of acute cholecystitis. The misdiagnosis rate for similar diagnostic criteria was less than 3%<sup>3,4</sup> and perhaps such criteria might help Dr. Sain in distinguishing biliary colic from acute cholecystitis. As clinicians, we do not always have the luxury of a pathologist's report in making the decision of the appropriate therapy, and the timing of surgical intervention for acute cholecystitis must be based on a clinical diagnosis.

Finally, we should remind ourselves that what Dr. Sain regarded as "the current 'gold standard' for the treatment of gallstone disease" was viewed with much skepticism when it was first described in the last decade. The theoretically higher risk of complications in operating on an acutely inflamed gallbladder is real with inexperienced surgeons, but reasonable data, including ours, have accumulated to support the efficacy and safety of early laparoscopic cholecystectomy in experienced hands. Our study suggested that early laparoscopic cholecystectomy for acute cholecystitis may be as safe as, and definitely more economical than, delayed operation. To further elucidate the validity of this hypothesis, a prospective, randomized trial of early *versus* delayed laparoscopic cholecystectomy for treatment of acute cholecystitis was started in our department since November 1994. So far, 34 patients were randomized to early and 41 to delayed surgery. Conversion was required in 3 of 34 patients of the early group and 4 of 32 who had undergone delayed operation. There was no major complication during the laparoscopic procedures, but one patient in the delayed group had bile duct injury during open operation after conversion. Perhaps we may be in a better position to distinguish advanced surgical care from experimental adventure when the final result of this prospective, randomized trial is available.

## Reference

1. Lo C-M, Liu C-L, Lai ECS, et al. Early *versus* delayed laparoscopic cholecystectomy for treatment of acute cholecystitis. *Ann Surg* 1996; 223:37-42.
2. Rattner DW, Ferguson C, Warshaw AL. Factors associated with successful laparoscopic cholecystectomy for acute cholecystitis. *Ann Surg* 1993; 217:233-236.
3. Jarvinen HJ, Hastbacka J. Early cholecystectomy for acute cholecystitis: a prospective randomized study. *Ann Surg* 1980; 191:501-505.
4. Norrby S, Herlin P, Holmin T, et al. Early or delayed cholecystectomy in acute cholecystitis: a clinical trial. *Br J Surg* 1983; 70:163-165.

CHUNG-MAU LO, M.B.B.S.(HK), F.R.C.S., F.R.A.C.S.  
Hong Kong