the clinician prognostic information that will accurately predict the aggressive phenotype for both node-positive and node-negative patients. Only when there is integration of these data will decisions relative to the administration or deletion of adjuvant therapies gain scientific credibility.

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Dear Editor:

We have read the interesting review article in which Kuo and Schroeder said: "Nitric oxide (NO) is a highly reactive free radical with a multitude of organ specific regulatory functions."[1(p220)]

The continuous and the more and more complex reviews about NO[1–4] are a great challenge when an attempt is made to integrate its diverse functions into the mechanisms that produce the greater part of the physiologic and pathologic conditions in the human organism.

We recently proposed[5] that in injuries caused by an old stimulus such as mechanical energy, the organism response or acute inflammation is composed of three successive phases based on the predominant expression of functions belonging to the nervous, immune, and endocrine systems. Essentially, sensitive (pain and analgesia) and motor (contraction and relaxation) symptoms and signs are produced in the first or nervous phase. In the intermediate or immune phase, the molecular (edema) and cellular infiltration (especially by neutrophils) of the tissues stands out; in the last or endocrine phase, repair changes, *i.e.*, anabolism and tissular regeneration or wound repair, predominate if the evolution has been favorable.

This abstraction also can be applied to the endothelium. In this case, vasoconstriction (ischemia) and vasodilation (revascularization) represent the nervous or immediate phase of the inflammatory response, exudation (edema) and diapedesis make up the immune or intermediate phase, and proliferation with endothelium and vascular wall modelling is the endocrine or late phase. These phases of expression of the inflammatory phenotype by the endothelium[6] also can be applied to local (wounds) or systemic (polytraumatized patient) traumatisms. In the latter case, ischemia–revascularization changes secondary to shock, the systemic inflammatory response syndrome with multiorgan failure and convalescence represent the succession of the three aforementioned partial responses in which the stimulation or inhibition of the nervous, immune, and endocrine functions, respectively, predominates. In this case, the response would be similar to that which already has been described in acute local inflammation. This hypothetical similarity of local and systemic responses can be attributed to the existence in the organism of a general response mechanism to injury by mechanical energy, which is based on the successive and predominant expression of the nervous, immune, and endocrine functions. In this case, these different forms of expression of this local or general response would have the same meaning.[5]

In the three phases of the inflammatory response mediators of the nervous, immune, and endocrine systems, that would predominately express the functions attributed to each phase, could act. This would explain the fact that one mediator by itself participates in different phases of this response. Particularly, NO, *i.e.*, a pluripotential molecule, can fulfill the requirements to be integrated in this three-phase response. Thus, in a first immediate or nervous phase, NO is a mediator of analgesia,[2,3,7] contraction or relaxation of the vascular smooth muscle,[3,4] myocardial contractility,[1] bronchodilation, relaxation of gastrointestinal smooth muscle, and neurotransmission.[1–4] In the intermediate or immune response to injury, this molecule would be involved in capillary permeability, platelet adhesion and aggregation, and leukocyte adhesion.[1,3,4] Finally, in the late or endocrine phase, NO regulates endothelial regeneration and smooth muscle cell proliferation.[1,3,4]

Essentially, if the final functions of each hypothetical phase of the response to injury could be used to propose a functional concept of the nervous, immune, and endocrine systems, it would be possible to integrate the biochemical knowledge about the mediators of inflammation into the functional meaning that each system has.

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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.

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March 11, 1996

Dear Editor:

I read the article by Lo and others[1] 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.[2] 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.[3] 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 ± 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 > 10×10^9/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.[4] 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