Nitric Oxide and Impaired Oxygenation before and after Liver Transplantation

To the Editor: Rolla and colleagues (1) reported that the increase in exhaled nitric oxide (NO) concentration after liver transplantation was correlated with improvement in oxygenation. Their conclusion that NO is an important mediator of impaired oxygenation in patients with cirrhosis is supported by other data (2, 3). However, their conclusion that “most cases of abnormal oxygenation in patients with cirrhosis are reversible after transplantation” may not be true.

First, Rolla and colleagues’ patients were not always hypoxemic, and the authors did not indicate the reversibility of abnormal oxygenation in patients with cirrhosis. Second, the hypoxemic patients with liver cirrhosis did not always demonstrate improved oxygenation after liver transplantation (4). Several investigators have reported that NO inhalation improved postoperative hypoxemia after liver transplantation for hepatic dysfunction associated with hepatopulmonary syndrome (4). Because this syndrome occurs secondary to functional right-to-left shunting caused by intrapulmonary vascular dilatation (5), inhaled NO may benefit patients who have increased shunt flow in the better-ventilated lung. This is why the decrease in exhaled NO concentration after liver transplantation was significantly, but not strongly, correlated with the decrease in alveolar–arterial oxygen gradient (r = 0.56; P = 0.014) (1), whereas previous data from the same authors suggested that exhaled NO output was strongly correlated with the decrease in alveolar–arterial oxygen gradient in patients with liver cirrhosis who have not had liver transplantation (r = 0.78; P < 0.001) (2).

Because portal hypertension, which leads to intrapulmonary shunting, plays an important role in the hepatopulmonary syndrome in patients with liver disease, the role of NO in oxygenation may differ among patients with compensated cirrhosis, decompensated cirrhosis, and the hepatopulmonary syndrome (3). Thus, the improvement of oxygenation in liver disease after liver transplantation may depend on the degree of intrapulmonary shunting and portal hypertension rather than on the production of NO in the lungs.

In response: Teramoto and colleagues question our conclusion that most cases of abnormal oxygenation in patients with cirrhosis are reversible after liver transplantation. We defined oxygenation abnormality as an increase in alveolar–arterial oxygen gradient greater than 15 mm Hg, which was present in 11 patients before and in 4 patients after liver transplantation (P < 0.05). We think our data justify this conclusion. Moreover, Battaglia and colleagues (1) have obtained similar results. That some patients with hepatopulmonary syndrome develop profound, early postoperative hypoxemia (which has been reported to improve after NO inhalation) does not contradict the postulated effect of endogenous NO in determining hypoxemia in cirrhosis. Exhaled NO represents endogenous production throughout the respiratory system, whereas NO administered by inhalation may shift blood flow from nonventilated to ventilated lung units accessible to NO (2).

In a previous study (3), we found a correlation between alveolar–arterial oxygen gradient and respiratory NO output before liver transplantation. Teramoto and colleagues state that this correlation is stronger than the correlation we had previously found between the decrease in alveolar–arterial oxygen gradient and exhaled NO concentration after liver transplantation. To properly make such a comparison, one must consider the different measurement units of exhaled NO used in our two studies. In particular, NO output takes into account minute ventilation, which is related to NO production (4).

We agree with Teramoto and colleagues that the improvement in oxygenation after liver transplantation depends on the decrease in intrapulmonary vasodilatation and portal hypertension, both of which are related to NO production (4).

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References
Psychotherapy for Depression in Diabetes

To the Editor: Lustman and colleagues’ trial (1) on the use of cognitive behavior therapy (CBT) for depression in type 2 diabetes raises several methodologic and ethical questions. As was noted in the accompanying editorial (2), no true control group was used. Specifically, because both the CBT group and the “control” group received diabetic counseling, while only the CBT group was exposed to depression-specific treatment, the comparison boiled down to CBT versus nothing.

In this way, the authors have failed to truly examine the effectiveness of CBT. What they have shown is that CBT is literally better than nothing in patients with diabetes. A true trial would compare CBT to sham therapy (nontherapeutic time with a therapist) or, better yet, to the gold standard of treatment: major depression, pharmacotherapy. It is entirely possible that the CBT group improved secondary to more time spent with a sympathetic ear, rather than any unique components of CBT.

The trial also did not answer the meaningful clinical question: Should I treat my depressed diabetic patients with CBT or with an antidepressant? One cannot conclude that because pharmacotherapy is better than placebo and because CBT is better than doing nothing that CBT is as effective as pharmacotherapy.

Finally, because no clinical question was truly answered and no one would contend that the diabetic counseling is effective therapy for depression, I am troubled by the ethics of randomly assigning 26 patients with major depressive disorder to receive no treatment. We know that depression is a painful, debilitating, and deadly disease, for which proven effective treatment (pharmacotherapy) exists. This allocation would be akin to withholding hypoglycemic therapy from diabetic patients, at the risk of complications, to study the effect on their depressive symptoms.

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References

To the Editor: Lustman and colleagues (1) compared CBT to no specific antidepressant treatment in diabetic patients with depression. Antidepressant medical therapy is the standard of care for the treatment of depression, and in an earlier study Lustman and colleagues reported that nortriptyline is effective for depression in diabetic patients (2). The design of this recent study is therefore ethically problematic in that the investigators withheld treatment from half of the participants. Although the investigators state that pharmacotherapy for depression may be poorly tolerated or insufficient in diabetic patients, this fact does not justify lack of treatment. Rather, as a rule, use of a no-treatment or placebo group is ethically appropriate only when no standard, effective therapy is available (3).

At the conclusion of Lustman and colleagues’ study, patients who remained depressed were offered pharmacotherapy or psychotherapy. This prompts an important question: If an intervention was clinically indicated for these depressed patients at the completion of the study, why was some form of therapy not appropriate for all of them at the inception of the study? In addition, in order for patients to provide fully informed consent to serve as study participants, they must be made aware of the alternatives to being enrolled in a research protocol. It is unclear from the Methods section of the paper whether the investigators made the study participants aware at the outset of the study of the alternative option of pharmacotherapy. Research in mental health is fraught with difficulty, and we commend the authors for identifying an important topic requiring scientific scrutiny. However, patients with mental illness may be particularly vulnerable to abuse as research participants, and thus we must take great care to ensure the ethical design of clinical trials in this field.

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References

In response: Approximately 2 out of every 3 depressed diabetic patients seen in the primary care setting receive no specific antidepressant treatment (1). This may be because their depressive disorders are not diagnosed and thus their physicians accept depression as an inevitable outcome of chronic illness, or because too little is known about the efficacy of treatments for depression in diabetes. In our 10-week clinical trial, half of the patients received supportive care for depression provided in the context of diabetes education, and half received supportive treatment plus CBT. Earlier controlled studies had found that supportive care provided in the context of health education was effective for postnatal depression (2). Thus, our participants were given more treatment than that often provided depressed diabetic patients, and each received a treatment with some evidence of efficacy. Several safeguards were used to protect participants during the trial, regardless of treatment assignment.

Concluding that ethical standards demand conventional antidepressant treatments for all participants at this point is premature because the efficacy of these treatments in diabetic patients has not been convincingly established. Generalization from the psychiatric treatment literature may be unsafe. Depression in diabetes appears in some ways different from depression in otherwise medically well patients. The cause may be different, with greater relative contributions from organic and psychosocial sources. The course is also decidedly different and is influenced by medical factors (for example, glycemic status). Findings from animal studies suggest the possibility of a resistance to conventional antidepressants in depressed diabetic patients (3). Diabetes frequently results in lifestyle restrictions, financial strain, pain, and disability, realities that may influence the course and limit the effectiveness of treatment. Consequently, for a variety of reasons, neither pharmacologic nor nonpharmacologic approaches can be considered effective at face value in the diabetic patient, and treatment versus no-treatment comparisons remain the scientific gold standard for establishing their utility.

Furthermore, whether random assignment to a no-treatment condition is ethically defensible depends, in part, on the efficacy of existing treatment; the more effective the treatment, the more inappropriate is its withholding (4). The potency of antidepressant treatment in nondiabetic samples is modest at best, the probability of depression remission being just 25% greater in those who receive active treatment over those who do not (5). In 40% of treated patients, depression does not remit. With such small margins of benefit and high rates of nonresponse, improper conclusions from trials lacking no-treatment control conditions are easy to envision. Active treatments might be considered comparable when neither or only one truly exceeds the expectations of placebo. It is the responsibility of the scientific community to determine the efficacy of treatment before issuing recommendations for such a prevalent problem.

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Coronary Thrombolysis: A Double-Edged Sword?

To the Editor: Gurwitz and colleagues (1) present important clinical information showing that the risk for hemorrhagic stroke increases as one moves from a clinical trial setting to a usual-care setting. These findings are all the more disturbing if one considers the following: First, the benefit (absolute risk reduction) of thrombolytic therapy is itself small, in absolute numbers ranging from 3% to 6%. Therefore, even a small, in absolute terms, increase in risk can rapidly undermine benefit because that benefit is also small. Second, with respect to mortality, only patients who would have died without thrombolytic therapy (10% to 15%) can benefit from thrombolytic therapy, whereas everyone who is treated is subjected to the risk for side effects. Therefore, most hemorrhagic strokes occur in those who will not benefit from treatment, at least with regard to mortality. Finally, the usual-care setting in this registry is itself selective, suggesting that in general use the benefit of thrombolytic therapy could be further compromised.

Although earlier and more widespread use of thrombolytic therapy is necessary if we are to save more lives, Gurwitz and colleagues’ results (1) underscore the fact that the therapeutic benefit of these agents is frail (only a few percentage points) and can be undermined rapidly if we are not careful.

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Reference

In response: Coronary thrombolysis remains one of the most effective treatments for reducing mortality rates in the setting of acute myocardial infarction. Using the absolute risk reduction estimates presented by Dr. Kessler, 17 to 33 patients who appear to be having an acute myocardial infarction must be treated to save 1 life. Such numbers are generally considered favorable in comparison with other medical interventions. However, as Sackett and colleagues have written, the number needed to treat (NNT) is a measure with real meaning for clinicians in caring for populations but not for individual patients (1).

Not every patient who is treated with thrombolytic therapy will benefit; every patient who is treated will be subjected to the risks associated with this treatment, and a few will sustain serious adverse effects. Coronary thrombolysis is a double-edged sword (2). Practical information on risk factors for the occurrence of intracranial hemorrhage with thrombolytic therapy is necessary to assist clinicians in making decisions about optimal patient selection for treatment. To increase the appropriate use of thrombolytic therapy in eligible patients and to optimize its benefits, clinicians must possess the knowledge to assess which edge of this sword is sharper.

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References
Elevated International Normalized Ratio Associated with Trovafloxacin

To the Editor: The international normalized ratio (INR [normal ≤ 1.0]) may become elevated in patients receiving trovafloxacin. We report four cases of elevated INR related to trovafloxacin.

Case 1: A 69-year-old woman was admitted with recurrent nephrolithiasis. At admission, her INR was normal. She was treated with cefepime for presumed pneumonia, but her condition worsened. Cefepime therapy was discontinued, and intravenous trovafloxacin therapy, 200 mg every 24 hours, was started. After 3 days of trovafloxacin treatment, her INR markedly increased to 5.26. Trovafloxacin therapy was discontinued, and her INR returned to normal in 3 days.

Case 2: A 29-year-old woman presented with appendiceal abscess. Her INR at admission was normal. Intravenous trovafloxacin therapy, 300 mg every 24 hours, was initiated. Two days later, her INR was 4.22. Trovafloxacin treatment was discontinued, and her INR became normal in 2 days.

Case 3: A 54-year-old diabetic man presented with cellulitis. At admission, his INR was normal. Intravenous trovafloxacin therapy, 300 mg followed by 200 mg every 24 hours, was begun, and 2 days later his INR was markedly elevated at 6.22. Trovafloxacin therapy was stopped, and his INR normalized after 2 days.

Case 4: An 80-year-old woman presented with substernal chest pain; her medications included aspirin and warfarin. Myocardial infarction was ruled out, but the patient developed nosocomial pneumonia and began receiving piperacillin and tazobactam. After 4 days, her INR was a therapeutic 2.23. Piperacillin and tazobactam treatment was discontinued, and intravenous trovafloxacin therapy, 300 mg every 24 hours, was started. After the first trovafloxacin dose, the INR increased to 5.6 even though the patient had not received warfarin for 3 days; trovafloxacin treatment was then discontinued. There were no signs of clinical bleeding, but the patient was treated with four units of fresh frozen plasma. Her INR returned to a therapeutic level of 2.5 after 2 days.

These cases should alert the physician to the potential anticoagulant effect of trovafloxacin. High intraluminal concentration of unchanged trovafloxacin (43%) via the gut may affect the intestinal microflora that produce vitamin K (1–4). The package insert for trovafloxacin does not mention prolongation of the INR. For patients receiving trovafloxacin, we obtain the INR daily. The INR normalizes after trovafloxacin therapy is stopped. Increased INRs may occur anytime during therapy or even after a single dose. Trovafloxacin should be used with caution or discontinued in patients who may have bleeding disorders.

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References

Tardive Dyskinesia Associated with Olanzapine

To the Editor: Tardive dyskinesia is the most feared side effect of prolonged neuroleptic treatment (1). The new atypical antipsychotic agents are supposed to reduce the incidence of tardive dyskinesia. Olanzapine, for example, may also help alleviate pre-existing symptoms of this condition (2). We report two cases of tardive dyskinesia that developed after olanzapine use.

Patient A was a 30-year-old woman with schizophrenia. She had moderate rigidity and akinesia and clinical features of residual schizophrenia (apathy, anhedonia). Her global score on the Positive and Negative Syndrome Scale (3) was 60; this reflected mild psychopathology. She was being treated with haloperidol, 10 mg/d. In view of her Parkinsonism and negative symptoms, her psychiatrist stopped haloperidol therapy and initiated treatment with olanzapine, 10 mg/d. Two months later, the patient developed involuntary perioral movements (moderately lateral jaw movements). Her total score on the Abnormal Involuntary Movement Scale (AIMS) (4) was 5 (moderate). The olanzapine dosage was increased; 6 months after the introduction of this drug, the dosage was 30 mg/d. The increased dosage did not improve her dyskinetic movements or her behavioral problems, and she was admitted to the hospital. Haloperidol, 6 mg/d, and trihexyphenidyl, 6 mg/d, were added to olanzapine, 20 mg/d. Two months after discharge from the hospital, the movements remained unaffected (AIMS score, 5).

Patient B, a 65-year-old woman, had residual schizophrenia. She had been taking fluphenazine decanoate (25 mg/mo). Because of the patient’s negative symptoms (emotional blunting, inactivity, apathy), her psychiatrist prescribed olanzapine at a dosage as high as 10 mg/d. Three months later, fluphenazine therapy was discontinued, and the olanzapine dosage was increased to 20 mg/d. Negative symptoms improved slightly, but 7 months later the patient developed athetoid movements of the tongue and chewing movements of the jaw. Two months later, therapy with olanzapine was discontinued and clozapine treatment (up to 100 mg/d) was started. Three months after clozapine therapy was started, neither negative symptoms nor dyskinetic movements had improved.

No cases of tardive dyskinesia related to this drug have been described previously. The cases reported here meet Diagnostic and Statistical Manual of Mental Disorders IV criteria of tardive dyskinesia and began 2 (patient A) and 7 months (patient B) after discontinuation of classic neuroleptic therapy. This suggests that tardive dyskinesia was not produced by the withdrawal from previous antipsychotic therapy.

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References

Do-Not-Resuscitate Orders in Radiology Departments

To the Editor: It was with great interest that I read Heffner and Barbieri’s report on compliance with do-not-resuscitate (DNR) orders for hospitalized patients transported to radiology departments (1).

As the authors noted in the Discussion section of the paper, and as it was hinted from the responses (questionnaire item 4),...
the lower compliance with DNR orders is probably associated with events occurring during invasive procedures. A written protocol for managing DNR orders and a formal procedure for receiving DNR status information, as they suggested, would clearly help minimize the problem. However, radiologists should also make every effort to communicate with patients (or the next of kin) about the possible complications of invasive procedures. This communication should (whenever possible) go beyond the usual informed consent to involve discussion of different scenarios, including what the patient might consider an acceptable resuscitation measure. This should not replace the communication between the patient and his or her primary physician about code status; rather, it would complement that discussion and help clarify DNR orders related to an invasive procedure. It could also help establish a closer relationship among the radiologist, the patient, and his or her family and assist the radiologist, when an emergency arises, to provide the level of care that is in accordance with the patient’s wishes. No note on the chart should describe and clarify the patient’s wishes for resuscitation better than can the patient.

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Reference

In response: We appreciate Dr. Mylonakis’ comments and agree with the recommendation that radiologists discuss end-of-life issues with their patients before invasive procedures. Management of DNR orders in the operating room is analogous in some respects to the transport of patients with a DNR status to the radiology department. Recent guidelines emphasize the importance of honoring DNR orders or negotiating with patients temporary DNR modifications during surgical procedures (1, 2). All recommended options emphasize the importance of physician–patient discussions that clearly establish the planned responses to life-threatening events before transfer to the operating room (3, 4). Our study indicates that the surveyed radiology departments rarely informed patients of departmental resuscitative practices even though 24% of programs would overrule DNR orders. Only 8.3% of programs that overruled DNR orders advised their patients of this practice.

Unfortunately, other investigations indicate that sole reliance on physician-initiated discussions is unlikely to safeguard patients’ end-of-life wishes. Most physicians, whether they are radiologists or primary care clinicians, do not discuss with their patients the likely outcomes of resuscitative interventions or explore their patients’ life-sustaining care preferences (5). It appears that policies, physician prompts, local “issue champions,” alterations of institutional culture, and other yet to be designed interventions are needed to facilitate patient–physician communication. Our study noted that the presence within radiology departments of a formal DNR protocol increased the likelihood that patients would be informed about resuscitative policies.

Our study, however, did not indicate that low compliance with DNR orders applied only to patients undergoing invasive procedures. Any patient transported to the radiology department was at risk for unwanted resuscitation. This conclusion was supported by the observation that unawareness of patients’ DNR status was the most commonly cited reason for performing CPR.

In the final analysis, our study was performed within radiology departments for reasons of feasibility, but we suspect that its observations apply to other locations within medical centers where patients with DNR orders are transported. Clearly, physicians should anticipate life-threatening events during patient transport and discuss with their patients the appropriateness of resuscitative responses in different circumstances. It appears, however, that maintenance of patient autonomy at the end of life may depend on institutional approaches to communicate and implement patient wishes across all areas of care. Otherwise, it may be unsafe for our patients who decline resuscitative care to leave their hospital rooms.

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References

Contemplating the White Coat

To the Editor: Wear (1) and Branch (2) have contributed thoughtfully to the discussion of values in medicine and their inculcation. Wear rightly argues that the white coat ceremony, or ritual, and the subsequent wearing of the white coat by student-physicians may hinder the development of the self-reflective skills critical for the cultivation of virtues intrinsic to the practice of medicine. She recommends “creating new rituals” around “community-based sites” where caregivers might model for student-physicians the virtues in medicine. Branch, on the other hand, suggests the importance of creating a forum for reflection among students who sense their values eroding during their training. Underlying both perspectives, I submit, is the question: How do we cultivate the virtuous physician?

Aristotle tells us that to become virtuous, we must practice virtuous actions. Virtuous actions are not merely those of a certain kind (potentially virtue-producing actions); they are characterized, among other things, by an understanding of why the action is done (3). I argue that the cultivation of the virtuous physician must include, as Wear suggests, the opportunity for student-physicians to participate in service—in potentially virtue-producing actions. But what is needed for virtue-producing actions is, as Aristotle suggests, understanding—in contemporary language, a progressive awareness of self that permits an individual to integrate the experiences of service, ritualized or not. Branch’s suggestion for a forum for reflection is a step in that direction, but I would hope for yet another: Why not encourage student-physicians to regularly cultivate the personal practice of self-reflection that leads to a deeper understanding of who they are and what motivates them? Why not encourage student-physicians to engage their own faith traditions, which have provided opportunities for self-reflection through prayer and meditation? Why not, at least, entertain the possibility of instructing student-physicians in the more secular versions of eastern and western meditative practices that for centuries have served to bring human beings to a greater level of self-transcendence from which the virtues flowed more naturally? Without self-reflective skills, without a deeper awareness of self, ritualized service experiences—indeed, any of life’s experiences, including that of wearing a white coat (or a clerical collar)—will be like seeds (of virtue) falling on concrete.

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References
To the Editor: Dr. Wear has written an interesting and provocative article on white coats and professional development (1). It took me back to my medical school days of 1936 to 1940. I must admit that a long white coat with a stethoscope peeping shyly from a side pocket made me feel rather medically grown-up.

But the significance of the white coat was much greater and more practical. 1) Often it was supplied by the hospital, which in Depression days was a real plus. 2) With a clean shirt, a bow tie (worn instead of a necktie, which would droop into blood and urine and onto the patient in the course of the day’s activities), and a pair of trousers presentable from the knees down, one could look reasonably professional on a budget that allowed but a minimal wardrobe. 3) Finally, the assorted stains, spills, and accidents in the course of a day of clinical study were absorbed by the white coat, which was then laundered at the hospital’s expense.

After graduation came postgraduate training, a stint in the Navy, and finally 40-plus years of the practice of internal medicine. During these years I continued to wear the white coat for many of the same reasons I did in medical school. I also found that humanism, altruism, and compassion come with the wearer and not the coat.

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Reference

To the Editor: The essays by Wear (1) and Branch (2) prompted me to reflect on my own professional development. Dr. Branch correctly notes that requiring students to visit community agencies or participate in other activities may be counterproductive. The problem is well summarized in his final paragraph. Little is known about the transition from student to fully mature physician; we generally negotiate this journey on our own. My experiences with housestaff have shown me that new physicians still face this journey with little guidance. Some never learn how to come to grips with their power, and few have a chance to discuss how their patients see them, the loneliness of responsibility, or what it means to make a mistake. We fall back on what we learned in the informal curriculum to deal with these issues. I agree: We should have more white coat ceremonies.

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Reference

In response: In response to Dr. De Marco, I certainly agree that understanding achieved through self-reflection underlies the physician who is virtuous, caring, and beneficent. It is my belief that successfully educating physicians in the human side of medicine requires a combination of activities, including self-reflection, alongside acquiring knowledge and skills, particularly in patient-physician communication. This was the purpose of the reflective component of the “Patient-Doctor” course at Harvard Medical School. However, the question arises of how much of one’s personal beliefs, religious faith, and preferences can be included officially in a medical school curriculum. It seemed to those of us who designed the “Patient-Doctor” course at Harvard that the reflective component in the curriculum ought to focus on professional interactions. There should be room for electives and voluntary endeavors outside the required curriculum for students who wish to go further in their process of self-reflection. I think that this would be all to the good and hope that it will occur if more attention is paid to the moral and humanistic aspects of medical care.

I agree with the sentiment of Dr. Paulsen’s letter but am saddened by the specter of loneliness he raises. Yes, another aspect of self-reflection is sharing some of the burdens of becoming a physician with trusted colleagues, all of whom have similar burdens. The transition from student to fully mature physician has been lonely for many and should not be so.

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Correction: Update in Pulmonary Medicine

In the recent Update in Pulmonary Medicine (1), the term “Löeffler syndrome” was used incorrectly on page 809. The sentence should read “Up to 15% of cases begin acutely with the Lofgren syndrome: erythema nodosum and bilateral hilar lymphadenopathy.”

Reference

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