

*Editorials***A NEW WEB SITE AND A NEW POLICY**

THE *Journal* has been on the World Wide Web for more than five years.<sup>1</sup> During that time, rapid, global dissemination of new scientific information has come to be expected. Broad searches of the medical literature and of scientific data bases are now possible. Information on line is becoming highly interlinked and increasingly is available in multimedia formats. To serve the diverse needs of our readers, we are taking steps to use the technology of electronic publication to enhance and complement the print version of the *Journal*. However, the many new electronic possibilities must not obscure our fundamental goal: to communicate the best in medical information in a way that physicians will find useful as they provide care for their patients.

This week, visitors to the *Journal's* Internet site (<http://www.nejm.org>) will see that it has been expanded and redesigned. It may take users some time to become familiar with the new site, but they should find many substantial improvements. For example, it will be easier to see at a glance what is in the current issue. There are now collections of articles, including Original Articles, Special Articles, review articles, and editorials published since 1996, organized under 51 topics. There are more links from articles to related materials, including summaries and related articles in the *Journal* and in Medline.

An improved search system makes it possible to search the full text of all *Journal* articles as far back as 1993, and one can now search specifically for figures or Images in Clinical Medicine. Abstracts of *Journal* articles are available from 1975 on. Users can now track where an article has been cited and go directly to the sources of the citations. Users can also sign up for e-mail alerts when a given article is cited in the future. The new Web site has been created in conjunction with Stanford University's High-Wire Press, and it is therefore possible to search more than 240 medical and scientific journals hosted there (including 8 of the 15 journals most often cited by articles in the *Journal*).

With the new Web site has come a major change in our publishing policies. Beginning six months after publication, the full text of all Original Articles and Special Articles will be available on line for free. For nonsubscribers, a brief, one-time registration is required to gain access to the full text of past research articles and to receive the table of contents each week by e-mail. However, nonsubscribers no longer have free access to editorials, Sounding Board articles, and letters to the editor. These articles will be available for a fee, and there is now an option to purchase access to the site for 24 hours.

After an initial registration, *Journal* subscribers will have access to all the features of our improved site, as well as to every article published since January 1993. The Web site will recognize the passwords of subscribers who have registered previously. Articles released early on the Web because they contain information of immediate clinical importance will continue to be available at no charge, as will all abstracts. The *Journal* has a strict policy regarding privacy, so no information about visitors' use of the site will be sold or shared with any commercial enterprises.

Our new policies relate to the steps taken by the National Institutes of Health over the past two years to create a public repository for the full texts of articles from biomedical journals (<http://pubmedcentral.nih.gov>). Although the Internet makes it possible to create such a centralized electronic archive, PubMed Central has been slow to grow and so far includes fewer than 10 journals. Concern has been expressed about the effects that an open, government-run archive might have on journals.<sup>2-5</sup> Offering free on-line access to the *Journal's* archives of research articles is a way to balance the goal of open communication with our publishing obligations. It should be possible someday to establish a single, searchable archive of biomedical-research reports in a way that does not threaten the peer-reviewed journals that help create the literature. We believe our commitment to providing the full texts of past research articles without charge is a step toward a useful central way to search the biomedical literature.

For the first time, advertising will appear on the *Journal's* redesigned Web site. Commercial advertising is present on the Web sites of some, but not all, medical journals. Because we believe electronic publication of scholarly material will have to become economically self-sufficient if it is to survive and grow, we are adopting policies that are consistent with those that are in effect for advertising in the print version of the *Journal*.

Over the past three years, the number of users of the *Journal's* Web site has increased by a factor of more than five. Each week more than 250,000 people visit this site. About 75 percent of these visitors are not subscribers, and more than half of the visits originate outside of North America. The objective of the new Web site is to communicate what we publish in a way that users will continue to find useful and convenient. We invite comments on both the new site and our electronic-publication policies.

EDWARD W. CAMPION, M.D.  
KENT R. ANDERSON  
JEFFREY M. DRAZEN, M.D.

**REFERENCES**

1. Campion EW. The *Journal's* new presence on the Internet. *N Engl J Med* 1996;334:1129.

2. Roberts RJ, Varmus HE, Ashburner M, et al. Building a "GenBank" of the published literature. *Science* 2001;291:2318-9.
3. Is a government archive the best option? *Science* 2001;291:2318-9.
4. Butler D, Campbell P. Future e-access to the primary literature. (See <http://www.nature.com/nature/debates/e-access/introduction.html>.) (See NAPS for 2 pages, c/o Microfiche Publications, 248 Hempstead Tpke., West Hempstead, NY 11552.)
5. Mellman I. Setting logical priorities. *Nature* 2001;410:1026.

Copyright © 2001 Massachusetts Medical Society.

## EXPANDING INDICATIONS FOR BETA-BLOCKERS IN HEART FAILURE

FOR more than a century, clinicians have noted that tachycardia, cutaneous vasoconstriction, diaphoresis, and reduced urinary output are cardinal manifestations of severe heart failure and surmised that these findings are caused by increased adrenergic activity. Armed with what was then a newly developed fluorometric assay for catecholamines, our group reported in the *Journal* almost 40 years ago that in patients with heart failure, plasma norepinephrine concentrations are elevated,<sup>1</sup> whereas cardiac stores of the neurotransmitter are reduced.<sup>2</sup> We postulated that the neurotransmitter exerts a positive inotropic effect by stimulating the failing myocardium and that the vasoconstriction induced by its action helps to maintain the perfusion of the vital organs when cardiac output is markedly reduced.<sup>3</sup> This hypothesis was subsequently supported by the observation that the short-term administration of beta-blockers sometimes causes a life-threatening intensification of heart failure in patients with severe forms of this condition.<sup>4</sup>

It is now clear that the interaction between the adrenergic nervous system and the failing heart is more complex than was first realized. Specifically, chronic overexposure of the heart to norepinephrine causes hypertrophy, ischemia, and myocyte damage.<sup>5</sup> The theory that the adrenergic nervous system has a maladaptive role in chronic heart failure is also supported by the salutary effects of beta-blockade on clinical outcome. Indeed, three large, randomized, placebo-controlled trials — the U.S. Carvedilol Heart Failure Trials Program,<sup>6</sup> the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure Study,<sup>7</sup> and the Cardiac Insufficiency Bisoprolol Study II<sup>8</sup> — were stopped early because of large reductions in mortality in the active-treatment groups. In a meta-analysis of 22 trials involving 10,135 patients with heart failure, the odds ratio for death was 0.65 with beta-blockers and the odds ratio for hospitalization for heart failure was 0.64.<sup>9</sup> These ratios translate into 3.8 lives saved and 4 hospitalizations avoided for every 100 patients treated for one year. Similar results were obtained with selective ( $\beta_1$ -receptor-specific) and nonselective blockers.

Have we made a 180-degree turn in our thinking

about beta-blockers and heart failure since the 1960s? Not quite. In all the aforementioned trials, the beta-blockers were administered orally and in gradually escalating doses, a strategy consistent with our understanding of the support of the failing heart by the adrenergic nervous system.<sup>3</sup> In addition, the three large clinical trials<sup>6-8</sup> were conducted in patients with mild-to-moderate heart failure, and only 5 percent of the patients included in the meta-analysis were classified as having New York Heart Association (NYHA) class IV heart failure.<sup>9</sup>

In this issue of the *Journal*, two groups of investigators report on the effects of beta-blockade in more severe heart failure. On first examination, these two trials appear to have come to opposite conclusions. The Carvedilol Prospective Randomized Cumulative Survival Study<sup>10</sup> enrolled patients with dyspnea or fatigue at rest or on minimal exertion and with a left ventricular ejection fraction of less than 25 percent. This trial was also stopped early because of a significant positive effect of the drug on survival. To place this trial in perspective, two points deserve emphasis. First, the beneficial effects of carvedilol were also observed in a subgroup of patients in the trial who were at the highest risk, defined as those with a left ventricular ejection fraction of 15 percent or lower or at least three hospitalizations for heart failure in the previous year. Second, patients with the most advanced forms of heart failure were excluded. Among these were patients with cardiac-related rales, ascites, or more than minimal edema despite treatment with diuretics; patients who required intensive cardiac care; and patients who had a serum creatinine concentration that exceeded 2.8 mg per deciliter (248  $\mu$ mol per liter). Thus, this trial included patients who might be characterized as having severe but not extremely severe heart failure.

The Beta-Blocker Evaluation of Survival Trial (BEST) randomly assigned patients with NYHA class III and class IV heart failure to placebo or the beta-blocker bucindolol.<sup>11</sup> Although the survival analysis showed a trend in favor of the beta-blocker, it was not statistically significant. This result is surprising in the face of all the other trials, but it is not really as jarring as it first appears. First, the confidence interval around the primary end point of death from any cause overlaps those of the other trials. Second, an improvement in survival with bucindolol was actually observed in nonblack patients, who comprised a large majority of those enrolled in previous trials. Finally, results for many of the important prespecified secondary end points also favored bucindolol, which led to reductions in the rates of death from cardiovascular causes, the combined end point of death from any cause or cardiac transplantation, and hospital admission for heart failure; there was also a marked improvement in the left ventricular ejection fraction.

One curious finding in this trial was that black pa-