

EDITORIALS



Embryonic Stem-Cell Research — The Case for Federal Funding

Jeffrey M. Drazen, M.D.

In the debate between those who support federal funding for embryonic stem-cell research and those who do not, a critical point has been overlooked. Research using this technology is strongly supported in a number of countries, including Australia, Israel, the Czech Republic, Singapore, Korea, and the United Kingdom. Others in the world appreciate the potential of this technology. If we continue to prevent federal funds from being used to support this research in the United States, the ability of our biomedical scientists to compete with other research teams throughout the world will be undermined. No matter how hard we try, we cannot legislate an end to a process of discovery that many in this country and elsewhere in the world consider ethically justifiable. The work will go on — but outside the United States.

The example of a single disease, diabetes, suggests the range of possibilities. Suppose that next week a group announced that it had successfully performed experiments showing that genetically identical pancreatic beta cells could be grown in tissue culture with use of a donor nucleus from a patient and human embryonic stem cells. If our working community of biomedical scientists had experience with this technology, it would probably take three to six months for the findings to be replicated; without the needed laboratory know-how, as a result of our current federal policy of permitting research with only a limited number of preexisting embryonic stem-cell lines, these experiments could take years to complete, and replication would be likely to happen outside the United States.

The next critical step would be to show that the pancreatic beta cells could be expanded *ex vivo* to achieve adequate numbers for transplantation and injection into patients with diabetes, where they

would “cure” the patients’ diabetes. For the data to be convincing, small trials would need to show that the cells functioned as desired for 6 to 12 months in a small number of patients. Again, for this research to be successful, the physicians and scientists who could create and expand the cell lines would need to be trained and ready to participate. Without an experienced workforce, years could be added to the time required. More than likely, such experiments would have to be conducted outside the United States.

Next, a major clinical trial would need to be mounted. The technology to create the cells for transplantation would have to be expanded to many centers, quality-control measures would need to be put in place, patients recruited, beta-cell lines created, cells injected, and patients followed for at least 30 months. Early research would probably use surrogate end points, such as glycosylated hemoglobin levels; studies with adequate power to detect differences in clinical end points, such as the development of renal failure or vascular events, would take much longer. As a conservative estimate, if the fundamental breakthrough at the laboratory level occurred next week, it would be more than five years before there was a stem-cell–based cure for diabetes. Without federal funding for stem-cell research, a prerequisite to the availability of a well-prepared research workforce, these experiments would probably be conducted outside the United States.

Although five years may seem like a long time, on the scale of therapeutic development it is relatively short. If we fail to bring the necessary research technology into the mainstream now, our children and grandchildren may need to leave the United States to benefit from treatments other nations are

currently developing. Our research scientists must be able to adopt and use embryonic stem-cell technology as they pursue its use in the treatment of many degenerative diseases. Such research has promise, but it must be nurtured to flourish.

We hope that the advances resulting from stem-cell technology will bring new tools to medical care. In the hypothetical example described above, progress in research would be reported at each step. As

journal editors, we undertake to review dispassionately any work on stem cells that is submitted to us. We pledge to report true advances. But for us to do so, the journey must be started. As each significant step brings us closer to the goal, we will be there to report the progress; it would be nice if some of this progress could be made within the United States.

Copyright © 2004 Massachusetts Medical Society.

Chemoradiotherapy for Rectal Cancer — When, Why, and How?

Robert D. Madoff, M.D.

Although colon cancer and rectal cancer share many features, clinicians should be aware of important differences in the clinical behavior and treatment of these two distinct diseases. Prominent among these is the tendency for rectal cancer — but not colon cancer — to recur locally. Local recurrence of rectal cancer is often catastrophic: it is difficult to cure, and the associated symptoms are debilitating. Accordingly, preventing local recurrence is one of the main goals of rectal-cancer treatment.

In 1990, a National Institutes of Health consensus conference recommended postoperative adjuvant chemoradiotherapy for patients with stage II rectal cancer (node-negative disease with transmural invasion) and stage III rectal cancer (node-positive disease).¹ At about the same time, the critical significance of proper operative technique was becoming apparent: pathology studies had demonstrated the importance of clear circumferential resection margins,² and clinical trials showed very low local recurrence rates after surgery alone.³ Indeed, precise anatomical excision of the rectum and its mesentery (a technique called total mesorectal excision) is now considered the cornerstone of adequate treatment for rectal cancer, and adoption of this technique on the national level has led to impressive improvements in both the rate of sphincter preservation and that of local recurrence.⁴

Ironically, at a time when official National Institutes of Health recommendations called for postoperative chemoradiotherapy and some surgeons called for no radiotherapy at all, a case began to build for preoperative radiotherapy. Preoperative radiotherapy is enticing for a number of reasons: the theoretical advantage of irradiating tissue not rendered hypoxic by previous surgery; the possibil-

ity of enhancing sphincter preservation by shrinking large distal tumors; the decreased likelihood of radiation-induced injury to small bowel trapped in the pelvis by adhesions; the ability to excise the irradiated large-bowel segment and perform an anastomosis with healthy colon to achieve better postoperative function; and the increasing accuracy of preoperative staging by endorectal ultrasonography.

Data supporting the use of preoperative radiotherapy in patients with rectal cancer have been steadily accumulating. The Swedish Rectal Cancer Trial showed that preoperative radiotherapy decreased the rate of local recurrence and improved the survival rate.⁵ However, patients in that trial did not uniformly undergo total mesorectal excision, and rates of local recurrence were relatively high both with and without radiotherapy. More recently, the Dutch Colorectal Cancer Group showed that preoperative radiotherapy decreased the local-recurrence rate even in patients who underwent total mesorectal excision, although no significant effect on survival was noted at two years' follow-up.⁶

In both the Swedish and the Dutch trials, preoperative radiotherapy was administered without chemotherapy in daily fractions of 5 Gy over a five-day period (total dosage, 25 Gy) — a common approach in Europe. In contrast, radiotherapy in the United States is generally administered in daily fractions of 1.8 to 2.0 Gy, five days per week, over a period of five to five and a half weeks (total dose, 45 to 50 Gy); chemotherapy is concurrently administered as a radiation sensitizer, most commonly with continuous-infusion fluorouracil. The U.S. (long-course) and European (short-course) radiation dosages seem disparate at first glance, but in