to the prostate and, thus, prostatic neoplasm. The use of magnetic resonance imaging (MRI), the use of urethrogram combined with CT, or *dynamic* urethrography, may be alternatives to the definition of the inferior portion of the prostate, and we agree with Roach that further investigations would be beneficial.

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VASOACTIVITY, A POTENTIALLY IMPORTANT VARIABLE IN THE SEQUENCING OF TIRAPAZAMINE (SR 4233) AND RADIATION

To the Editor: In their article describing the time course of tumor reoxygenation following tirapazamine (SR 4233, 3-amino-1,2,4-benzotriazine-1,4 dioxide), Kim and Brown (10) suggest that "maximum interaction" between the drug and radiation should occur when the former is administered at some point prior to irradiation. However, it would appear that further data on the vasoactive properties of tirapazamine are needed before the most appropriate time for tirapazamine administration can be determined for clinical studies.

Conventional chemotherapeutic agents such as mitomycin C and doxorubicin can markedly alter tumor blood flow and modulate hypoxia (8). Such alterations may be significant when chemotherapy is combined with irradiation. It has been postulated that the inferior local tumor control seen in patients with cervical tumors who were treated with the radiosensitizer pimonidazole (11) could have been due to the increase in tumor hypoxia produced by this vasoactive agent (4). In murine tumors, the bolus administration of cisplatin increases tumor blood flow for up to 30 min (3), a fact that may partly explain the finding that improved local tumor control in nonsmall cell lung tumors was seen only when cisplatin was administered daily before irradiation as opposed to other schedules (12).

In a murine tumor, a mean reduction of tumor blood flow to approximately 50% of control values was observed at 4–5 h following the bolus administration of tirapazamine (5). As this was only observed in two of four experiments, the authors cautioned that the finding was not conclusive proof for the vasoactivity of tirapazamine itself. Nevertheless, a more complete characterization of the time course with earlier time points could have revealed significant changes in blood flow in the other two experiments. When combined with external radiotherapy, a bolus dose of tirapazamine produced maximal *in vivo* cell killing when administered 30 min before radiation (2). With progressively shorter intervals, cell killing decreased until it was close to that consistent with an additive effect when the two modalities were timed together. Postirradiation administration of tirapazamine resulted in an increase in cell kill, a finding suggesting that a drug-induced increase in tumor hypoxia cannot be excluded. Similarly, the yet unexplained tumor-specific, schedule-dependent interaction between cisplatin and tirapazamine (7) could be a consequence of the vasoactive properties of both drugs.

In clinical studies (6), tirapazamine was administered at a constant rate of infusion (3.5 mg/min) and any decrease in tumor blood flow could result in longer periods of hypoxia. Further investigations are particularly necessary as another nitroxide (RB-90003X), which is also undergoing evaluation as a hypoxic cytotoxin, has been reported to reduce tumor blood flow (detected by laser doppler) and also produced ^{31}P magnetic resonance spectra changes consistent with reduced tumor oxygenation (1).

Considerable heterogeneity for hypoxia exists in human tumors with only one-third of breast tumors showing low pO_2 levels of between 0 and 2.5 mm Hg (i.e., less than half-maximum radiosensitivity) (13). Similarly, hypoxic regions were only detected in 21 of 31 patients with cervical tumors who were also evaluated using computerized polarographic electrodes (9). As there is currently no reliable noninvasive system to determine the extent of tumor hypoxia in individual tumors, the benefits of a hypoxic cytotoxin may be diminished if it compromises radiation-induced aerobic cell kill in tumors without significant pretreatment hypoxia. To a lesser extent, inappropriate timing could also compromize cell kill in tumors with significant numbers of hypoxic cells.

Given the evidence for the vasoactivity of nitroxides, it is clear that the data from the available preclinical studies of tirapazamine cannot be used to predict the optimal schedule in combination with irradiation in clinical studies.

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