commercial insurance ($p = 0.01$),[4] less pulmonary disease ($p = 0.01$), and a high incidence of benign disease (most recently 26% at Hopkins).[5] Thus, we believe the operative mortality rate after Whipple resection in Maryland was *not* reduced, but merely *redistributed*, by this very effective regionalization program and stand by our conclusion quoted by Drs. Gordon and Burleyson.

Especially in this current era of managed care, claims of superior outcomes must be balanced against the numerous, inherent, and variable risks in the patient population.[1] The advantages of risk avoidance surely are clear to Dr. Gordon, the Vice President for Planning and Marketing for the Johns Hopkins Health System.

References

1. Houghton A. Variation in outcome of surgical procedures. Br J Surg 1994; 81:653–760.
2. Gordon TA, Burleyson GP, Tielsch JM, Cameron JL. The effects of regionalization on cost and outcome for one general high-risk surgical procedure. Ann Surg 1995; 221:43–49.
3. Wade TP, El-Ghazzaway AG, Virgo KS, Johnson FE. The Whipple resection for cancer in U.S. Department of Veterans Affairs hospitals. Ann Surg 1995; 221:241–248.
4. Hadley J, Steinberg EP, Feder J. Comparison of uninsured and privately insured hospital patients. JAMA 1991; 265:374–379.
5. Cameron JL, Pitt HA, Lillemoe KD, et al. One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. Ann Surg 1993; 217:430–438.

TERENCE P. WADE, M.D.
FRANK E. JOHNSON, M.D.
St. Louis, Missouri

October 30, 1995

Dear Editor:

We read with interest the letter by Drs. Wade and Johnson regarding our study of Whipple resections at Maryland hospitals.[1] Based on the data we presented, they conclude that the operative mortality rate at Johns Hopkins Hospital was lower than at other Maryland hospitals because patients with lower risk of operative mortality were selected by Hopkins. We agree with their assertion that certain patient characteristics are associated with improved outcome. However, the significantly lower mortality ($p < 0.001$), length of stay ($p = 0.05$), and hospital charges ($p < 0.001$) at Hopkins remained after we adjusted for differences in age, race, gender, source of payment, source of admission, and comorbidity. This led us to our assertion that regional medical centers, like Hopkins, have special expertise in procedures they perform in high volume.

Drs. Wade and Johnson also believe that "the operative mortality rate after Whipple resection in Maryland was *not* reduced, but merely *redistributed,* by this very effective regionalization program. . . ." We did not provide statewide mortality trends in our article. However, if redistribution of low-risk patients occurred, it would be expected that over time, Hopkins mortality would decrease, other hospital mortality would increase, and overall Maryland mortality would remain constant. Examination of the data, however, shows all three mortality rates have been decreasing while Hopkins' share of discharges has been increasing. In the first 6 months of 1995, 72% of Maryland patients undergoing the Whipple procedure were treated at Hopkins, and the statewide mortality rate was 5%. This is a substantial improvement on the 17% statewide mortality rate of 10 years ago, when Hopkins had only a 30% share of Maryland Whipple cases.

We believe that our study and the data that we have presented in this letter document the appropriate regionalization of care for one high-risk surgical procedure. The high-volume provider has increased its share of patients, reducing the statewide mortality rate. Although other providers have improved mortality rates over time, the most recent 6 months of data indicate that the relative risk of dying in a low-volume hospital is ten times greater (14.3% *vs.* 1.4%) than at the high-volume provider.

References

1. Gordon TA, Burleyson GP, Tielsch JM, Cameron JL. The effects of regionalization on cost and outcome for one general high-risk surgical procedure. Ann Surg 1995; 221:43–49.

TOBY A. GORDON, M.D.
GREGG P. BURLEYSON, R.N., M.H.S.
JAMES M. TIELSCH, PH.D.
JOHN L. CAMERON, M.D.
Baltimore, Maryland

June 30, 1995

Dear Editor:

We read with interest the article written by Deitch et al. regarding the effect of nutrition on intestinal epithelial barrier function.[1] Dr. Deitch and his coworkers present a very important study eliciting the role of nutrition-induced epithelial barrier failure for bacterial translocation. In contrast to chow-fed rats, rats fed intravenous total parenteral nutrition (IV-TPN) and elemental diet had bacterial translocation, as shown by histology and bacteriology.

However, methodologic considerations and suggestions concerning their interpretation of electrophysiological data have to be made.

Using Ohm's law, resistance was calculated from potential difference (PD)-deflection elicited by defined current pulses (50 μA). Because Ohm's law states: R = PD/I and current (I) is given in μA/cm2, resistance should be given in ohm $\times$ cm^2,[2,3] instead of ohm/cm^2, which would implicate Ohm's law as R = PD $\times$ I.

Corrections also should be made for general interpretation of electrophysiologic parameters made in the discussion.[1(p304)] Short-circuit current, but not potential difference (PD), represents a marker for active ion transport.[4] Potential difference measures the ability of the epithelium to separate charges.[3]

Finally, we do not fully agree with the interpretation of electrophysiology (Fig. 5, 6) and phenol red permeability data (Fig. 4) and the results obtained from *Escherichia coli in vitro* translocation assay (Fig. 3). Mucosal preparations obtained from rats treated with IV-TPN and elemental diet are traversed by *E. coli in vitro* (Fig. 3; 75% *vs.* 30% after 3 hours), whereas no translocation occurred in explants derived from chow-fed rats. Transepithelial permeability for phenol red, a marker for the paracellular pathway, was significantly increased in the IV-TPN group when compared with chow-fed rats and the elemental diet group (Fig. 4; 10% *vs.* 1% and 2%, respectively). These data indicate that increased transmigration of *E. coli* in IV-TPN *versus* elemental diet mainly is due to increased paracellular conductance. Thus, we suggest that *in vitro* transmigration of *E. coli* occurs via the transcellular route in the elemental diet group (low phenol red permeability) and via the trans- and paracellular route in the IV-TPN group (increased phenol red permeability). Because electrophysiology is a sensitive measure for epithelial barrier integrity, transepithelial PD and resistance (R) were assessed. From the above-mentioned data, we would expect normal resistance in chow-fed rats, decreased transcellular resistance (*i.e.*, increased transcellular conductance = secretion due to opening of ion channels) in elemental diet-fed rats, and decreased paracellular resistance (*i.e.*, decreased tight junction integrity) in rats fed IV-TPN. However, although all groups exhibited similar PD values (3 mV), resistance was lower in elemental diet and IV-TPN fed tissues (15 ohm $\times$ cm^2) (Fig 5, 6). According to Ohm's law, tissues exhibiting same PD values but lower resistances are expected to have increased short-circuit current (*i.e.*, active ion transport). Using the data shown in Figure 5 and 6 and Ohm's law, short-circuit current (ISC) is approximately 120 *versus* 200 μA/cm^2 in chow-fed rats *versus* rats fed elemental diet and IV-TPN. Thus, elemental diet and IV-TPN are supposed to induce secretion—*i.e.*, increased transcellular conductance.

In contrast to that, the authors suggest that elemental diet and IV-TPN did diminish active ion transport.[1(p304)] If this were true, we would expect higher resistances for elemental diet and IV-TPN tissues (*i.e.*, same PD and lower Isc).

Additional techniques would allow such discrepancies to be elicited: *e.g.*, dual sodium/mannitol flux studies represent an elegant approach to distinguish between increased trans- and/or paracellular conductance.[5] Such studies would then provide information about the route of bacterial translocation in *in vitro* models of epithelial barrier failure. However, electron microscopy and immunfluorescent investigations of the cytoskeleton[3,5] would enable us to gain more insights in morphologic events leading to nutrition-induced epithelial barrier failure.

Taken together, discrepancies exist between electrophysiology, permeability studies, and *E. coli* transmigration assay. Therefore, the main goal of the study remains open: how do IV-TPN and elemental diet induce permeability changes facilitating bacterial translocation? Via opening of the trans and/or paracellular pathway? In contrast to the interpretation given by the authors, we believe that their data demonstrate distinct routes of translocation in the elemental diet group *versus* the IV-TPN group. Increased Isc indicates that elemental diet and IV-TPN induce secretion—*i.e.*, they increase transcellular conductance. In contrast to elemental diet, IV-TPN also increased paracellular permeability, as indicated by transepithelial passage of phenol red. Therefore, we suggest that elemental diet facilitates translocation via the transcellular pathway, whereas IV-TPN enables bacteria to translocate para- and transcellularly. Additional *in vitro* studies will have to elicit structural and functional events leading to bacterial translocation.

References

1. Deitch E, Xu D, Naruhn MB, et al. Elemental diet and IV-TPN-induced bacterial translocation is associated with loss of intestinal mucosal barrier function against bacteria. Ann Surg 1995; 221:299–307.
2. Parkos AC, Delp C, Arnaout MA, Madara JL. Neutrophil migration across a cultured intestinal epithelium: dependence on a CD11/CD18-mediated event and enhanced efficiency in physiological direction. J Clin Invest 1991; 88:1605–1612.
3. Riegler M, Sedivy R, Pothoulakis C, et al. Clostridium difficile toxin B is more potent than toxin A in damaging human colonic epithelium *in vitro*. J Clin Invest 1995; 95:2004–2011.
4. Madara JL, Patapoff TW, Gillece-Castro B, et al. 5'adenosine monophosphate is the neutrophil-derived paracrine factor that elicits chloride secretion from T84 intestinal epithelial cell monolayers. J Clin Invest 1993; 91:2320–2325.
5. Madara JL, Barenberg D, Carlson S. Effects of cytochalasin D on occluding junction of intestinal absorptive cells: further evidence that the cytoskeleton may influence paracellular permeability and junction charge selectivity. J Cell Biol 1986; 102:2125–2136.

MARTIN RIEGLER, M.D.
THOMAS SAUTNER, M.D.
ETIENNE WENZL, M.D.
Vienna, Austria

November 3, 1995

Dear Editor:

Dr. Riegler questions our way of measuring membrane resistance. We measured membrane resistance and normalized the