Letter to the Editor

Etiologic Role of *Hafnia alvei* in Human Diarrheal Illness

I read with interest the article by Dr. Albert and colleagues presenting evidence for the association of *Hafnia alvei* with human diarrheal illness (1). The authors state that to their knowledge *H. alvei* has never been implicated as a causative agent of diarrhea. As far back as 1957, Harada et al. (3) reported isolating *Hafnia* species from two infants and a woman with vomiting and diarrhea. In 1961, on the basis of the results of toxicity tests with ligated rabbit intestine, Dr. Sakazaki reported that members of the genus *Hafnia* could possess diarrheagenic potential (5). In fact, a number of *Hafnia* isolates he tested were from diarrheic stools. There has been at least one other report suggesting a possible role for *H. alvei* in sporadic gastroenteritis (2), and our own report in 1979 incriminated *H. alvei* in a nosocomial outbreak of gastroenteritis (4). Although we were likely the first to report an outbreak of gastroenteritis associated with this agent, our findings did not appear in a refereed publication, and hence, I am including a brief account.

Two outbreaks of gastroenteritis occurred, a month apart, in a general hospital, affecting 15 inpatients in the first outbreak and 25 inpatients in the second outbreak. *H. alvei* (then referred to as *Enterobacter hafniae*) was isolated from stool cultures as either predominant or heavy pure growth from five of eight patients tested from the first episode and 8 of 15 patients tested during the second episode. Antibiotic treatment was excluded as a possible cause of diarrhea. Of 75 dietary staff screened by stool cultures, 3 yielded *H. alvei* in light and mixed growth, and all 75 were asymptomatic. None of the patients or the dietary staff was positive for commonly recognized enteric pathogens. Further studies with the *H. alvei* isolates from both episodes indicated that all belonged to a single biotype (biotype 1) and serotype (O3:H−). (It is worth noting that according to the antigenic schema reported by Dr. Sakazaki in 1961 [5], the Hafnia group consisted of 29 O groups, 23 H antigens, and 51 serotypes.) As with Dr. Albert's strain, all our isolates tested negative for heat-labile and heat-stable enterotoxins and for enteroinvasiveness. In addition, they also tested negative for Vero cytotoxin. *H. alvei* was not found in over 1,000 stool cultures monitored subsequent to the outbreaks except for a single instance a month later. *H. alvei* was isolated as a heavy pure growth in the absence of other enteric pathogens from a sporadic case of gastroenteritis within the hospital. This strain turned out to be biotype 9 and serotype O22:H−. Our observations clearly incriminated *H. alvei* in the outbreaks of gastroenteritis, although the source of the outbreak and its possible relation to food and food handlers could not be established conclusively.

There is no reliable data as to the true rate of isolation of *H. alvei* from clinical specimens in routine practice. While the generally known incidence is small, it is not known whether this might be due to lack of information on the clinical significance of this agent. It appears that *H. alvei* has a greater role in human diarrheal illness than currently recognized. It is important to recognize that, in spite of a virtual revolution in the ability to uncover and identify enteric pathogens in the recent past, clinical laboratories still do not come up with a specific etiologic diagnosis in the great majority of diarrheal cases. I concur with Dr. Albert and his colleagues that at least some strains of *H. alvei* have diarrheagenic potential, and there is a need to determine the relative importance of *H. alvei* in human diarrheal illness.

REFERENCES

1. **Albert, M. J., K. Alam, M. Islam, J. Montanaro, A. S. M. H. Rahman, K. Haider, M. A. Hossain, A. K. M. G. Kibriya, and S. Tzipori.** 1991. *Hafnia alvei*, a probable cause of diarrhea in humans. Infect. Immun. **59**:1507–1513.
2. **Emslie-Smith, A. H.** 1961. *Hafnia alvei* strains possessing the alpha antigen of Stamp and Stone. J. Pathol. Bacteriol. **81**:534–536.
3. **Harada, K., K. Shimizu, and T. Matsuyama.** 1957. Hafnia isolated from men. Gumma J. Med. Sci. **6**:109–112.
4. **Ratnam, S., R. W. Butler, S. March, S. Parsons, P. Clarke, A. Bell, and K. Hogan.** 1979. *Enterobacter hafniae*-associated gastroenteritis—Newfoundland. Can. Dis. Weekly Rep. **5**:231–232.
5. **Sakazaki, R.** 1961. Studies on the Hafnia group of *Enterobacteriaceae*. Jpn. J. Med. Sci. Biol. **14**:223–241.

Samuel Ratnam
Newfoundland Public Health Laboratory
St. John's, Newfoundland
Canada A1B 3T2

Author's Reply

I agree with the comment of Dr. Ratnam that there is a need to determine the relative importance of *Hafnia alvei* in human diarrheal illness. Also, Dr. Ratnam draws your attention to our statement that "to our knowledge it (*H. alvei*) has never been implicated as a causative agent of diarrhea" (1) and quotes some earlier studies which suggested a possible role for *H. alvei* in diarrhea. I wish to point out that most of the quoted studies were reported a long time ago in relatively inaccessible journals, and even according to the latest edition of *Edwards and Ewing's Identification of Enterobacteriaceae* (3) "members of this species are not known to be incitants of gastroenteritis." The study of Emslie-Smith (2) which Dr. Ratnam quotes used strains of *H. alvei* isolated from feces of patients suffering from gastroenteritis, and this study did not suggest that this organism was the cause of diarrhea. Even in Dr. Ratnam's study (5), no virulence property was demonstrated for the isolates. I did not have ready access to the Japanese reports (4, 6), and so I am unable to comment on them.

Ours was the first study (1) which reproduced diarrhea in whole-animal models and demonstrated the well-known pathogenic lesion of attachment-effacement as the basis of diarrhea. This report was based on a single isolate, and we have since isolated several strains of *H. alvei* from patients with diarrhea in the absence of well-recognized pathogens. All these strains possessed the attaching-effacing property found in the original isolate.

On the basis of our experience, I would like to alert other investigators to the possible role of *H. alvei* in human diarrheal illness.

REFERENCES

1. **Albert, M. J., K. Alam, M. Islam, J. Montanaro, A. S. M. H. Rahman, K. Haider, M. A. Hossain, A. K. M. G. Kibriya, and S. Tzipori.** 1991. *Hafnia alvei*, a probable cause of diarrhea in humans. Infect. Immun. **59**:1507–1513.

2. **Emslie-Smith, A. H.** 1961. *Hafnia alvei* strains possessing the alpha antigen of Stamp and Stone. J. Pathol. Bacteriol. **81**:534–536.
3. **Ewing, W. H.** 1986. Edwards and Ewing's identification of *Enterobacteriaceae*, 4th ed., p. 417–421. Elsevier, New York.
4. **Harada, K., K. Shimizu, and T. Matsuyama.** 1957. Hafnia isolated from men. Gumma J. Med. Sci. **6**:109–112.
5. **Ratnam, S., R. W. Butler, S. March, S. Parsons, P. Clarke, A. Bell, and K. Hogan.** 1979. *Enterobacter hafniae*-associated gastroenteritis—Newfoundland. Can. Dis. Weekly Rep. **5**:231–232.
6. **Sakazaki, R.** 1961. Studies on the Hafnia group of *Enterobacteriaceae*. Jpn. J. Med. Sci. Biol. **14**:223–241.

M. John Albert
International Centre for Diarrhoeal Disease Research, Bangladesh
Dhaka—1000, Bangladesh

U.S. Postal Service

STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION

Required by 39 U.S.C. 3685)

1A. Title of Publication	1B. PUBLICATION NO.	2. Date of Filing
Infection and Immunity	0 0 1 9 9 5 6 7	10-23-91
3. Frequency of Issue	3A. No. of Issues Published Annually	3B. Annual Subscription Price
Monthly	12	$45 mbr, $350 nonmbr

4. Complete Mailing Address of Known Office of Publication *(Street, City, County, State and ZIP+4 Code) (Not printers)*
American Society for Microbiology
1325 Massachusetts Ave., N.W., Washington, DC 20005-4171

5. Complete Mailing Address of the Headquarters of General Business Offices of the Publisher *(Not printer)*
(Same as above)

6. Full Names and Complete Mailing Address of Publisher, Editor, and Managing Editor *(This item MUST NOT be blank)*

Publisher *(Name and Complete Mailing Address)*
(Same as above)

Editor *(Name and Complete Mailing Address)*
Vincent A. Fischetti
(Address same as above)

Managing Editor *(Name and Complete Mailing Address)*
Linda M. Illig
(Address same as above)

7. Owner *(If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding 1 percent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address, as well as that of each individual must be given. If the publication is published by a nonprofit organization, its name and address must be stated.) (Item must be completed.)*

Full Name	Complete Mailing Address
American Society for Microbiology	1325 Massachusetts Ave., N.W.
	Washington, DC 20005-4171

8. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages or Other Securities *(If there are none, so state)*

Full Name	Complete Mailing Address
NONE	

9. For Completion by Nonprofit Organizations Authorized To Mail at Special Rates *(DMM Section 423.12 only)*
The purpose, function, and nonprofit status of this organization and the exempt status for Federal income tax purposes *(Check one)*

(1) [X] Has Not Changed During Preceding 12 Months
(2) [ ] Has Changed During Preceding 12 Months
(If changed, publisher must submit explanation of change with this statement.)

10. Extent and Nature of Circulation *(See instructions on reverse side)*	Average No. Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
A. Total No. Copies *(Net Press Run)*	8,242	7,500
B. Paid and/or Requested Circulation 1. Sales through dealers and carriers, street vendors and counter sales	—	—
2. Mail Subscription *(Paid and/or requested)*	6,114	6,555
C. Total Paid and/or Requested Circulation *(Sum or 10B1 and 10B2)*	6,114	6,555
D. Free Distribution by Mail, Carrier or Other Means Samples, Complimentary, and Other Free Copies	28	28
E. Total Distribution *(Sum of C and D)*	6,142	6,583
F. Copies Not Distributed 1. Office use, left over, unaccounted, spoiled after printing	2,100	917
2. Return from News Agents	—	—
G. TOTAL *(Sum of E, F1 and 2—should equal net press run shown in A)*	8,242	7,500

11. **I certify that the statements made by me above are correct and complete**

Signature and Title of Editor, Publisher, Business Manager, or Owner
Linda M. Illig Director, Journals

PS Form **3526**, Feb. 1989 *(See instructions on reverse)*