



## Mapping Cholera Research and the Impact of Sambhu Nath De of Calcutta\*

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Cholera is a disease that has plagued the world sporadically throughout history. The disease has assumed pandemic proportions, meaning it has spread rapidly over a very wide geographic area, on seven occasions since 1817. In many Third World nations, where sanitation is often poor and water supplies are frequently contaminated, cholera still rages practically unchecked. Despite advances in medicine and public health in recent years, the increased volume of international traffic has also increased the opportunity for cholera to spread beyond the endemic areas—those areas where cholera occurs regularly at a varying rate. Indeed, cholera is one of the six most formidable infectious diseases in the world today.<sup>1</sup>

In this discussion of cholera, I would like to pay tribute to the late Sambhu Nath De, professor emeritus, University of Calcutta School of Medicine, whose work with cholera paved the way to a more effective strategy for treatment and control. De was born in 1915 in Garbati, West Bengal. He received his PhD in 1949 from the University of London, after which he returned to India to become the first professor of pathology and bacteriology at the Nil Ratan Sircar Medical College. From 1955 until his retirement in 1973, De was director of pathology and bacteriology at the Calcutta Medical College.

### History

In his classic book *King Cholera: The Biography of a Disease*, medical historian Norman Longmate states that the term cholera was often used as early as 400 BC to describe any violent form of intestinal disorder. He notes that the first well-defined cholera pandemic began in August 1817 in what was then Jessore, India, and is now Bangladesh, 70 miles from Calcutta. The term "Asiatic cholera" was used to distinguish this malady from similar but distinct

diseases. After spreading through India, the disease moved across the Arabian Sea to the Middle East and into Russia. By 1832 nearly every European capital had been touched by Asiatic cholera<sup>2</sup> (p. 2–3). Worldwide cholera epidemics would recur six more times.

Currently in its seventh pandemic, cholera is endemic in a variety of countries across the globe. H. G. V. Küstner, state epidemiologist, Department of Health, Welfare, and Pensions, Pretoria, South Africa, and colleagues note that cholera has spread from Indonesia to Southeast Asia, the mainland of Asia, and through the Middle East, reaching Africa in 1970. Cholera was endemic in Malawi, Mozambique, and Angola by 1973.<sup>1</sup> Roger I. Glass, International Centre for Diarrhoeal Disease Research (ICDDR), Dacca, Bangladesh, and colleagues describe cholera as indigenous to Bangladesh.<sup>3</sup> In 1973 Jack B. Weissman, Centers for Disease Control (CDC), Atlanta, Georgia, and colleagues reported the first known case of cholera acquired in the US since 1911 in a resident of the Gulf Coast of Texas.<sup>4</sup> Wayne X. Shandera, CDC, and colleagues state that the disease is now apparently endemic along the US Gulf Coast.<sup>5</sup>

Two strains, or varieties, of *Vibrio cholerae* have been identified as the causative agents of cholera. *V. cholerae* is a comma-shaped bacterium discovered by German researcher Robert Koch in 1883.<sup>2</sup> (p. 225–6) The common variety of *V. cholerae* is thought to have been the major cause of epidemic cholera for the first six pandemics, although conclusive strain identifications are not available for the earlier pandemics. We will say more about the seventh pandemic later.

Spread by food and water contaminated by human excrement, *V. cholerae* thrives in the human digestive tract, where it multiplies and releases a poisonous substance known as an enterotoxin. This

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enterotoxin is bound to the intestinal lining, triggering hypersecretion of fluids in the intestine. Voluminous diarrhea, often followed by vomiting, drains as much as 25 percent of the body's fluids within hours and depletes the victim of essential salts. D. M. Mackay, deputy director, Ross Institute of Tropical Hygiene, London School of Hygiene and Tropical Medicine, warns that, without proper treatment, a victim faces dehydration, kidney failure, and circulatory collapse, resulting in a painful death.<sup>6</sup>

In 1959 De was the first to demonstrate that cholera bacteria secrete enterotoxin. This discovery eventually promoted research to find a treatment aimed directly at neutralizing the cholera enterotoxin. De's paper "Enterotoxicity of bacteria-free culture-filtrate of *Vibrio cholerae*,"<sup>7</sup> while initially unrecognized, today is considered a milestone in the history of cholera research. Biochemist W. E. van Heyningen, professor emeritus, University of Oxford, UK, and John R. Seal, former scientific director, National Institute of Allergy and Infectious Diseases, Bethesda, note that De's paper "deserves to go down as a classic in the history of cholera, and, indeed, as later developments have shown, in the history of cellular physiology and biochemistry."<sup>8</sup>

In 1905 a second cholera-producing strain, called *V. cholerae el tor*, was isolated. The characteristic differences between *V. cholerae el tor* and *V. cholerae* are not sufficient to justify their separation as two species. Consequently *V. cholerae el tor* is considered a biotype of *V. cholerae* — meaning that they both have the same genetic makeup. *V. cholerae el tor* is the primary cause of the present seventh pandemic, which began in Indonesia in 1961, virtually replacing *V. cholerae* as the main epidemic strain. However, A.R. Samadi, ICDDR, and colleagues note that as recently as 1982, *V. cholerae* is once again gaining advantage as the major cause of cholera.<sup>9</sup>

Mackay states that *V. cholerae el tor* is better able to survive in the environment than *V. cholerae* and causes a much wider spectrum of disease.<sup>6</sup> While *V. cholerae* causes patients to become immobilized, reducing their capacity for spreading the disease, the *El Tor* strain may cause many moderate cases, allowing the victims to move around with only mild discomfort. These victims then act as dangerous vectors of the disease. But not all cases of *El Tor* cholera are mild — a major infection with *V. cholerae el tor* has similar symptoms to *V. cholerae* and can be as fatal.

### Transmission

The mode in which cholera is spread has been the subject of dispute since the early 1800s, and the debate continues. Many models of cholera transmission support the waterborne transmission theory. As early as 1849, before germs had been recognized as the cause of disease, the London doctor John Snow

discovered that cholera is a waterborne infection.<sup>10</sup> Snow proposed that cholera is a contagious disease caused by a poison reproducing itself in the bodies of its victims and spreading through excretions and vomit that then contaminate the water supply. More recently, a team led by Moslem U. Khan, ICDDR, confirmed the close link between water used for drinking, bathing, and laundry and the risk of cholera. The authors suggest that the only effective means of control is a protected water supply and the prevention of contaminated water use.<sup>11</sup> I have recently discussed the use of chlorination in eliminating waterborne disease.<sup>12</sup>

Christopher J. Miller, Bohumil S. Drasar, and Richard G. Feachem, Ross Institute and Department of Medical Microbiology, London School of Hygiene and Tropical Medicine, reported that waterborne cholera transmission is associated with water salinities between 0.01 and 0.1 percent. These salinity limits, together with the seasonal fluctuations of estuarine salinities, may help explain the observed variation in the seasonal pattern of reported cholera cases.<sup>13</sup>

Epidemiologist Paul A. Blake, CDC, and fellow researchers have determined that contact with both contaminated water and food can spread cholera. In an investigation of a 1978 cholera outbreak along the Gulf Coast of Louisiana, Blake and colleagues determined the transmission vehicle to be cooked crabs from Louisiana marshes. A transmission mechanism was suggested that involved fecal contamination of marsh water by infected persons, contamination of crabs by the water, consumption of inadequately cooked contaminated crabs, and further human infection.<sup>14</sup>

### Treatment and Control

Cholera patients suffer so much fluid loss that, without treatment, they die from dehydration long before their bodies have time to mount an immune response to the infecting cholera bacteria.<sup>6</sup> Treatment includes replacement of lost fluids and infusions of salts to restore the body's water and chemical balance. This regimen is almost always effective, but without prompt medical attention, 58 percent of the victims die.

In the Third World, where cholera is most prevalent, an effective treatment must be simple, inexpensive, and available to large numbers of patients. One of the easiest methods of treatment is oral rehydration therapy. When properly used, this therapy can reduce the mortality due to cholera to less than 1 percent by replacing the essential fluids and salts lost during the severe diarrhea and vomiting associated with cholera. A. S. M. M. Rahman, ICDDR, and colleagues tested a solution of glucose-rich rice powder, salt, and boiled water that produced dramatic results.<sup>15</sup>

Antibiotics have had limited success in treating cholera. Used in conjunction with oral rehydration therapy, however, drugs help reduce the volume of fluid loss, the amount of replacement fluid necessary, and the duration of cholera bacteria excretion. P. G. Sen Gupta and his team from the Cholera Research Center, Calcutta, found that a single oral dose of the drug doxycycline is effective in significantly reducing the load of *V. cholerae* infection among contacts of cholera patients for up to five days following treatment.<sup>16</sup>

Epidemiological observations have pointed to the development of acquired immunity by individuals with cholera infection. W. H. Mosley, chief, Epidemiology Section, Pakistan-SEATO Cholera Research Laboratory, Dacca, and colleagues found that in endemic areas such as Bangladesh, the incidence of cholera is higher in children two-to-four years of age. The incidence diminishes in older age groups, while the cholera antibody that fights disease increases with age.<sup>17</sup>

Despite nearly a century of research, a satisfactory vaccine has not yet been developed. Initially, research focused on a vaccine that would stimulate the immune system to fight the cholera bacteria directly. Unfortunately, antibacterial cholera vaccines have a proven efficiency of only 40 to 80 percent for a short duration of three to six months.<sup>18</sup> However, thanks to De's discovery of the cholera enterotoxin, mentioned earlier, research has been redirected to find a vaccine that will spark the immune system to fight the enterotoxin specifically, rather than the bacteria.

James B. Kaper, Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, and colleagues describe a highly promising approach toward cholera vaccination.<sup>19</sup> Recombinant DNA techniques are used to construct a weakened or attenuated *V. cholerae* strain. The genes encoding toxin production are removed, while the genes encoding the antigens likely to be involved in immunity are preserved. This strain can then be administered as an oral vaccine, stimulating the development of antibodies to protect the body from future *V. cholerae* invasion while not producing the severe symptoms associated with the disease.

Khan and M. Shahidullah, ICDDR, advocate health education as a major factor in achieving the proper sanitation for lowering the incidence of cholera.<sup>20</sup> J. C. Azurin, director of quarantine, and M. Alvero, medical specialist, Joint Philippines/Japan/WHO Cholera *El Tor* Research Project, found that sanitation measures used in combination with an uncontaminated water supply reduced the number of cholera cases by 76 per cent.<sup>21</sup>

### Cholera Literature and Research Fronts

Since its first European outbreak in 1832, cholera has been well documented by social historians. In

1966 Charles E. Rosenberg, Department of History, University of Pennsylvania, Philadelphia, claimed that historical documentation of a disease "should provide materials for the construction of a cross-section of cultural values and practices at one moment in time. Values and attitudes, especially in the areas of science, or religion, of traditionalism and innovation are . . . inevitably displayed during an epidemic."<sup>22</sup>

Ten years later R. J. Morris, lecturer in economic history, University of Edinburgh, UK, noted that the response of nineteenth century society to cholera epidemics reveals the weaknesses and strengths of the society's administrators, policymakers, and physicians who were responsible for national action.<sup>23</sup> Morris believes that the literature concerning the social effects of cholera can be used in combination with our current knowledge about the disease to enable us to view the present pandemic with "humanitarian concern rather than with the alarm for our own safety which the nineteenth century felt."<sup>24</sup> This observation has relevance to today's AIDS epidemic.

The most recent cholera pandemic has provided an abundance of material for study of the disease using contemporary scientific methodology. The extensive investigations have resulted in an explosion of information containing new concepts about the pathogenesis, epidemiology, and treatment of cholera. Table 1 lists the most prominent journals that report

**Table 1:** Selected list of journals reporting on cholera. A = title. First year of publication is given in parentheses. B = 1984 impact factor.

A	B
American Journal of Epidemiology (1921)	2.39
American Journal of Tropical Medicine and Hygiene (1921)	1.56
Applied and Environmental Microbiology (1953)	1.95
Bulletin de la Societe de Pathologie Exotique et de ses Filiales (1908)	0.19
Bulletin of the World Health Organization (1947)	1.40
Gastroenterology (1943)	5.34
Indian Journal of Medical Research (1913)	0.24
Infection and Immunity (1970)	3.00
Journal of Infectious Diseases (1904)	3.47
Tropical and Geographical Medicine (1948)	0.28

on cholera, along with their 1984 impact factors. We derived this list by a combination of online and manual literature searches using keywords, concepts, prominent authors, and papers from the cholera field. This included core and citing papers from current cholera research fronts, as well as those cited in the books consulted for this essay. The final, carefully edited list is quite selective. As with many subjects, there is a wide dispersion of literature in hundreds of journals, but only a small number provide core literature. This list provides a wide geographic as well as an inclusive subject representation of facets of cholera research.

Great breakthrough overlooked or simply

of the existence of a cholera enterotoxin. The significance of De's discovery was not immediately grasped. His 1959 paper in *Nature* on the enterotoxicity of *V. cholerae*<sup>7</sup> went virtually unnoticed for at least five years. Indeed, we could find only three citations to this paper in the *Science Citation Index*<sup>®</sup> (*SCI*<sup>®</sup>) between 1959 and 1963. Today his paper has been explicitly cited in only 100 publications, but as noted earlier, it is the cornerstone of current anti-toxin vaccine research – and a classic example of delayed recognition.

There are some parallels between Barbara McClintock, the 1983 Nobel Prize winner in medicine, and De.<sup>25</sup> McClintock is prone to seclusion and intellectual isolation, as was De. But while McClintock was elected to the National Academy of Sciences, De was never elected a fellow of any Indian academy and never received any major award. Subbiah Arunachalam, editor, *Indian Journal of Technology*, New Delhi, told us that S. Sriramachari, director, Institute of Pathology, and additional director general, Indian Council of Medical Research, New Delhi, mentioned that De's contributions stand out as a pinnacle of excellence in our understanding of the pathogenesis of cholera. Sriramachari also mentioned the work of E. K. Narayanan of the Central Research Institute, Kasauli.<sup>26</sup> In the mid-1960s Narayanan made independent observations concerning the possible role of toxins of cholera vibrios.<sup>27</sup> Yet he also failed

to receive attention from his contemporaries.

In a paper presented at the annual meeting of the American Association for the Advancement of Science, Arunachalam reported that first-rate research performed by Third World scientists, even when published in respected international journals, is often overlooked by scientists in more advanced countries in favour of work reported later by other scientists from advanced countries.<sup>28</sup> This is a special variant of delayed recognition, a very broad subject that will be covered in the near future.

De and colleagues also published highly cited pioneering studies on *V. cholerae* action on the intestinal membrane.<sup>29-31</sup> The 1953 paper "An experimental study of the mechanism of action of *Vibrio cholerae* on the intestinal mucous membrane" is De's most-cited paper, cited 340 times since its publication.<sup>29</sup> De passed away just before we wrote to ask him for a *Citation Classic*<sup>™</sup> commentary. We hope that one of his colleagues will write one for him.

De's most-cited paper has been core to cholera research fronts for many years, including recent research fronts on "E. coli and *Vibrio cholerae* enterotoxin; detection, characterization, and role of adherence" (#83-2883) and "Characterization of cholera enterotoxin and other enterotoxins" (#84-4877). These two fronts are included in a historiograph in Figure 1 that shows the progression of cholera research. The fronts included in this figure

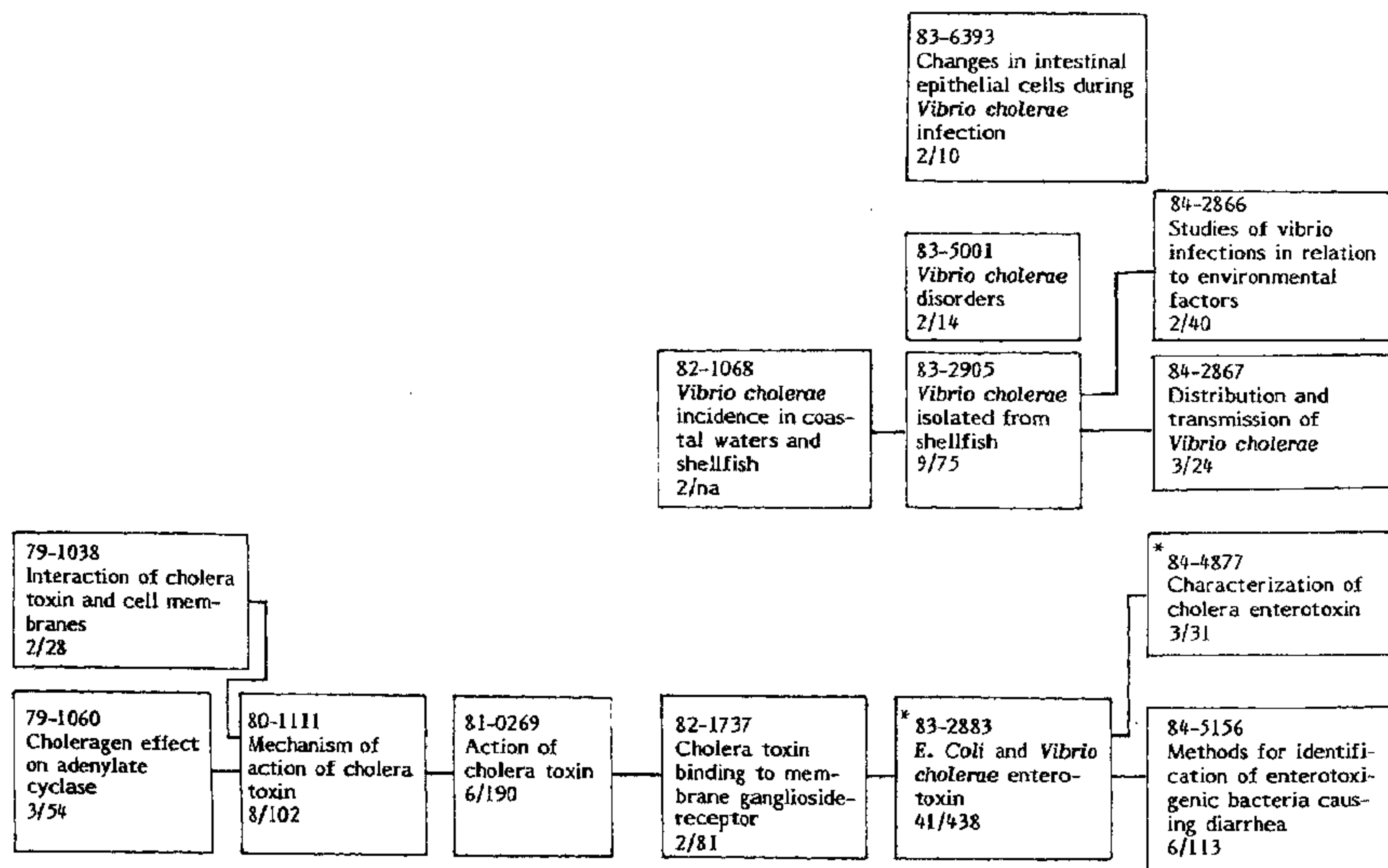


Figure 1. Historiograph tracing research on cholera toxin and *Vibrio cholerae* organism. Numbers at the bottom of each box refer to the number of core/citing papers for each research front. Asterisks refer to research fronts in which S. N. De has a core paper.

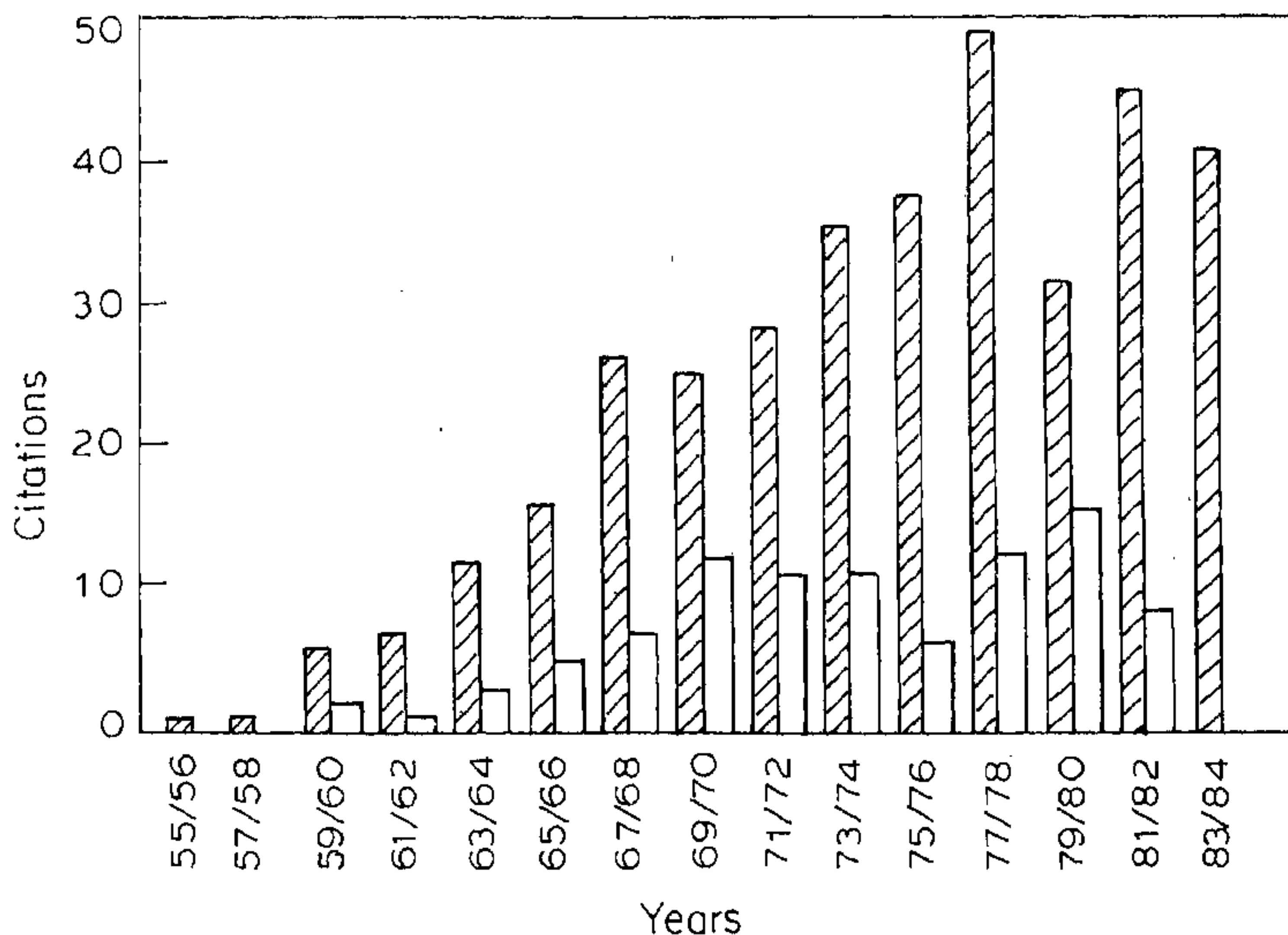
are determined by the continuity of the core literature from year to year. A list of cholera-related research fronts for 1983 and 1984 is shown in Table 2. Figure 2 shows a chronological distribution of citations to De's two most influential papers.

Figure 3 is a multidimensional-scaling map for the C2-level research front on "Aspects of *Vibrio cholerae* and *E. coli* enterotoxin" (#83-0355). This map shows the way in which many related fronts are linked by co-citation, including research front #83-

2883 (located in the center of the map), mentioned earlier as the front containing De's most-cited paper. Cholera research is part of a broader field of study concerning the effect of toxins produced by intestinal bacteria. This is illustrated in Figure 4, which is a 1984 C2-level map showing how cholera research has merged into many broader research fronts that do not deal with the cholera bacteria specifically, but instead relate to studies that further intestinal bacteria research.

**Table 2.** The 1983 and 1984 *SCI/SSCI* research fronts on cholera. A= number. B = name. C = number of core papers. D = number of citing papers.

A	B	C	D
83-2883	<i>E. coli</i> and <i>Vibrio cholerae</i> enterotoxin: detection, characterization, and role of adherence	41	438
83-2905	<i>Vibrio cholerae</i> and related species isolated from marine shellfish and sediment in the Gulf Coast United States	9	75
83-5001	Gastroenteritis, bacteremia, and other disorders from <i>Vibrio cholerae</i> and non-O1 vibrio infections	2	14
83-6393	Intestinal epithelial cells during <i>Vibrio cholerae</i> and <i>Salmonella</i> infection; changes in fine structure and fibronectin	2	10
84-2866	Studies of vibrio infections in relation to environmental factors	2	40
84-2867	Distribution, transmission, and isolated pockets of <i>Vibrio cholerae</i> and other strains of cholera	3	24
84-4877	Characterization of cholera enterotoxin and other enterotoxins	3	31
84-5156	Methods for identification of enterotoxigenic <i>E. coli</i> and other bacteria causing diarrhea	6	113



**Figure 2.** Chronological distribution of citations to two of S. N. De's most-cited papers. The shaded bar shows citations to his 1953 *Journal of Pathology and Bacteriology* paper; light bar shows citations to the 1959 *Nature* paper on *Vibrio cholerae* enterotoxin.

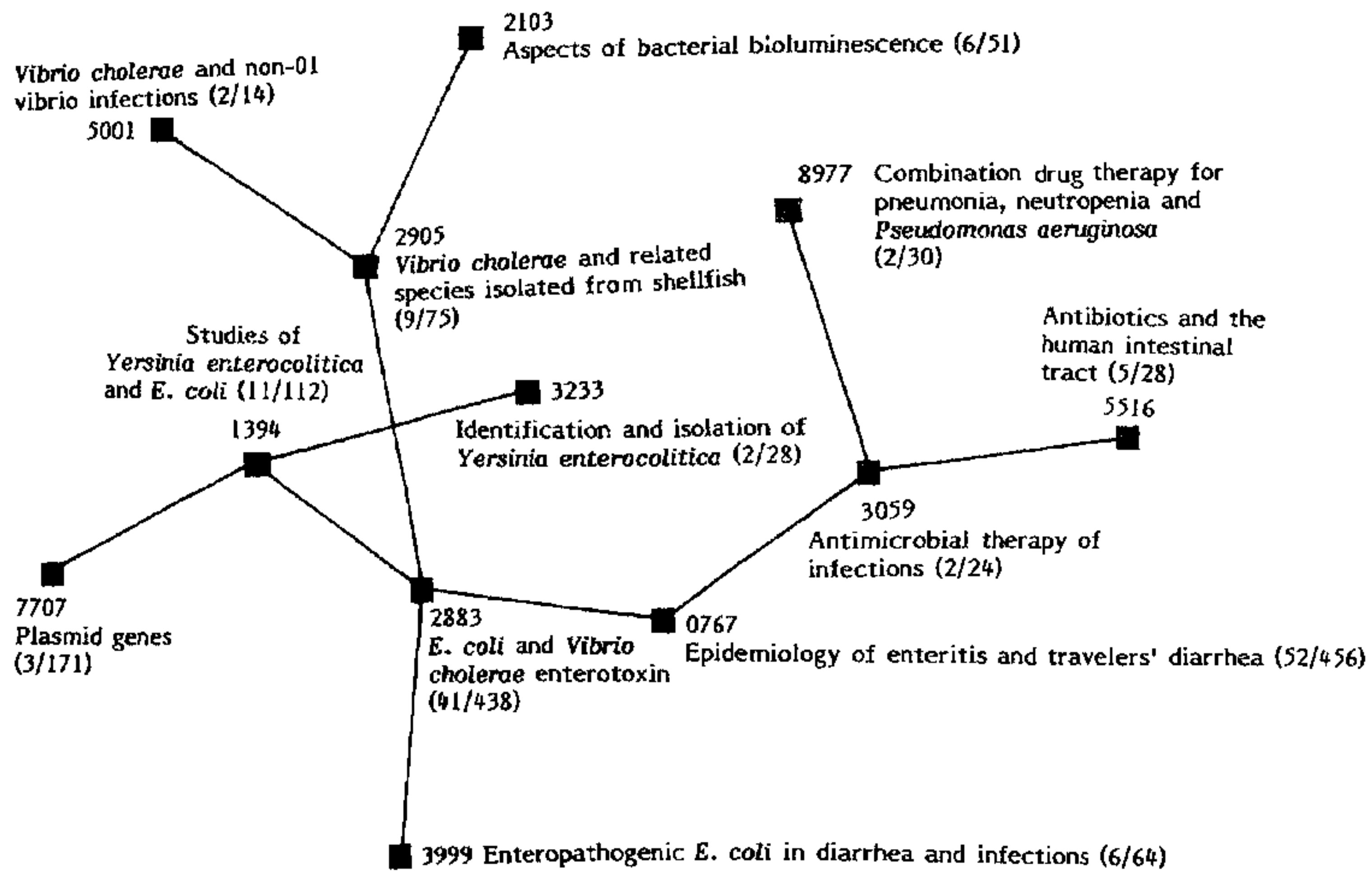


Figure 3. Multidimensional-scaling map for C2-level research front #83-0355, "Aspects of *Vibrio cholerae* and *E. coli* enterotoxin," showing links between C1 research fronts. Numbers of core/citing documents for each front are shown in parentheses after the research-front name.

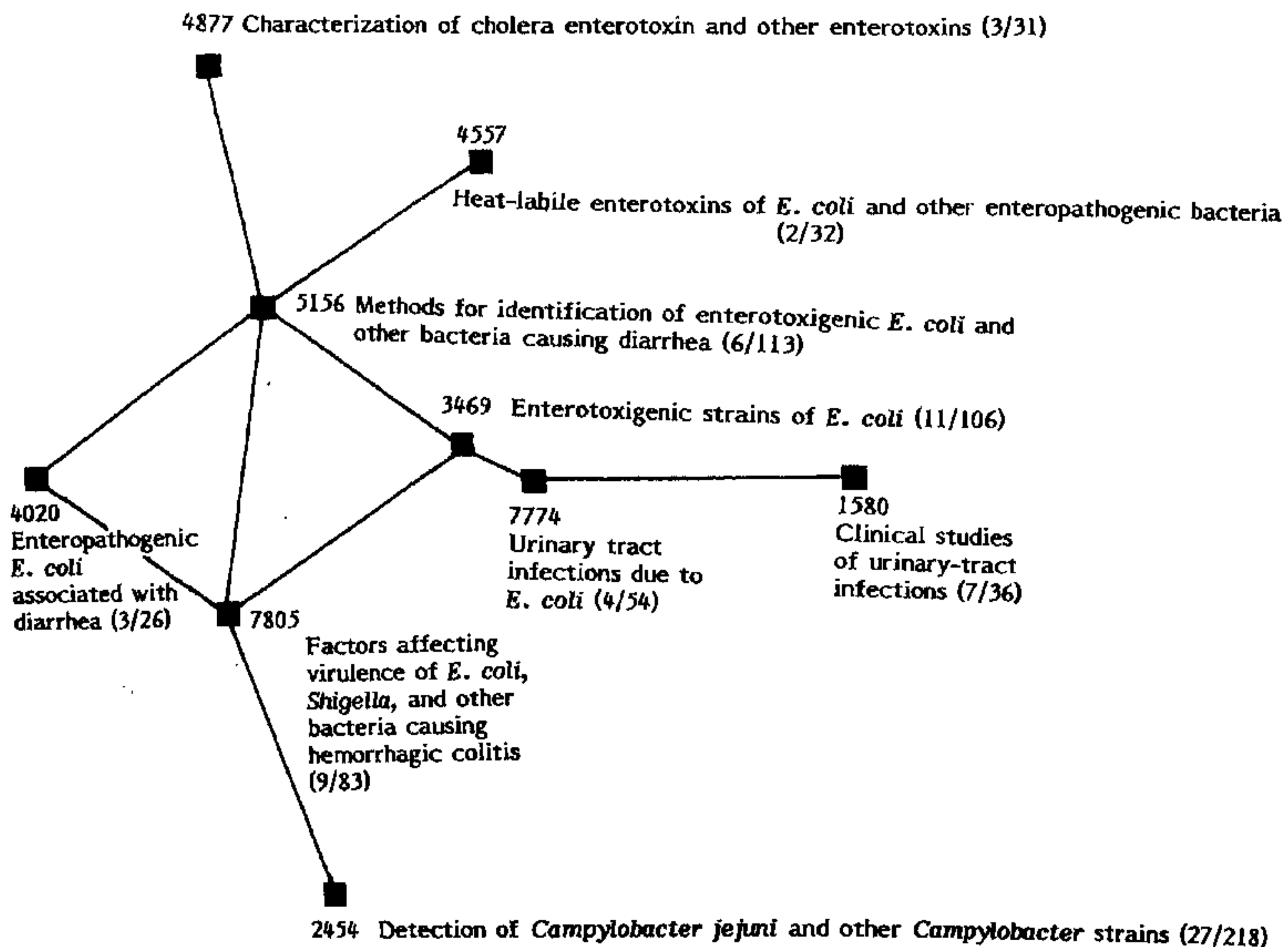


Figure 4. Multidimensional-scaling map for C2-level research front #84-0600, "Characterization of *Vibrio cholerae*, *E. coli*, and other enteropathogenic organisms," showing links between C1 research fronts. Numbers of core/citing documents for each front are given in parentheses after the research-front name.

## Conclusion

Cholera remains a chronic problem particularly in Third World nations. In previous essays we have discussed other diseases, such as schistosomiasis, common to the Third World.<sup>32</sup> Fortunately, the mortality rate of cholera can be virtually eliminated with a simple oral rehydration therapy. The real enemy is the ease with which cholera can be transmitted, and the seven pandemics in the last 150 years attest to the difficulty in containing the disease. Control will depend on educating the Third World populations in healthful sanitation methods that do not intrude on cultural or religious tenets and that therefore can be easily accepted.

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