S N De – An Appreciation

S N De's recognition that cholera is a toxinosis was the key which unlocked the doorway to our present understanding of the cellular and molecular events in cholera pathogenesis. Even more fundamentally, the event which preceded his recognition of the enterotoxin as the final expression of pathogenesis in this disease, was his development of the rabbit intestinal segment model. For seventy years following Koch's recognition that the cholera vibrio is the causative bacterial agent, other researchers had failed to produce a relevant model in which to study its pathogenic potential – that is, relevant to the human disease. De not only developed and perfected the model, he also used it and described it with such patient and painstaking skill that his colleagues throughout the world could continue the work he began with confidence and satisfaction.

In retrospect, many of us who have worked in this area took for granted the discovery and the perfection of this seemingly simple model system; but looking back, it seems the world needed the fertile mind of an investigator whose natural scientific instincts forced him to shun the conventional approaches to the study of infectious disease in animals, and aim straight for the organ, tissue and cells which are most clearly affected in this disease. No matter how simple it may now seem, we are compelled to recognize that his was a truly creative and novel piece of work, which started a chain of events which, in turn, forever altered our concepts surrounding the pathogenesis of secretory diarrhea.

On a personal note, I vividly and fondly recall the day in September, 1964, when I first met S N De in Calcutta. As a newcomer to the family of cholera buffs, I had read with fascination De's publications of the recent decade in which he described the exotoxic principle which he had recognized in the rabbit intestinal model. After having worked in nearby Dhaka for a few months on the vascular permeability factor in cholera stools. I was eager to talk with De about his work, and to seek his advice. Well do I remember his warm hospitality, collegiality, and generosity and his eagerness to share with me the excitement of his findings of the previous decade.

After comparing notes for several pleasant hours we decided that we were both probably working with the same toxic principle excreted by cholera vibrios, but observing its effects in

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two different tissues. Later, when the enterotoxin had been purified by others, this surmise on our part proved to be correct. In our conversation I realized that here was a colleague who really enjoyed more than anything else the quest for an understanding of Nature, and who thrilled to the exchange of experience and ideas with his fellow students. He was never aggressive in offering his findings to the scientific community, and, if there was delay in accepting his observations into the mainstream of scientific thought of the time, it was owing to the inertia of his colleagues in cholera, and not to an inadequate presentation of his findings to the biomedical community.

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The Discovery of Cholera Toxin

Koch, it may be remembered, had started his address to the first cholera conference in 1884 with the statement that little progress had been made in research on cholera during the preceding 10 years beause there had been no cholera in the countries where research on other infectious diseases had been advancing, and in India, where there was plenty of cholera there was nobody to do the research. In the first half of the twentieth century, cholera was no longer a serious problem in Europe and the stimulus to do research on it had died down. But in India, cholera never ceased to be a problem, and by the mid-century India had produced its own research workers, with abundant incentive to take action. The benefits of their work came just in time for the seventh cholera pandemic and the renewed interest in cholera in Western countries, mainly the United States of America.

In India, research on the cholera toxin problem advanced simultaneously and independently on two fronts in the 1950s in N K Dutta's laboratory in the Haffkine Institute in Bombay and in S N De's Department of Pathology of the Nilratan Sircar Medical College in Calcutta, on the other side of India. It was De, undoubtedly, who discovered cholera exotoxin, in 1959.

In 1953, De reinvented *de novo* the ligated intestinal loop of Violle and Crendiropoulo – "reinvented" rather than revived, because at the time De was unware of Violle and Crendiropoulo's 38-year-old short paper in the proceedings of the French Société de Biologie, which had rapidly sunk into obscurity (De, personal communication, 1978). It came to his notice only 8 years later, when he happened to read an abstract of it in the *Tropical Diseases Bulletin* of 1915. De did not explain, any more than Violle had, what led him to try ligated intestinal loops.

.... De made no comment in his paper on the question of cholera toxin, except (with every justification!) to use the title: "Enterotoxicity of bacteria-free culture filtrate of *Vibrio cholerae*". This short essay 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.

Excerpted from W E van Heyningen and J R Seal, *Cholera: The American Scientific Experience*, 1947–1980.