Special Issue on S. N. De and
Cholera Enterotoxin

S. N. De – Regicide of Reigning Dogma

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Intellectual life would not be possible without invoking a hierarchy of tested and trusted truths. We stand on the shoulders of giants[1] so as to see further. A relentless, nihilistic skepticism about the foundations of belief would leave no energy for more constructive activity. The essential tension in scientific innovation is the balance between imaginative creativity and critical rigor in the generation, than the validation of belief [2]. With good reason, there is a scientific establishment safeguarding the hard-won truths of reliable authority.

Joshua Lederberg, 'multidisciplinarian extraordinaire' is the outgoing President of The Rockefeller University, New York. Together with Edward L. Tatum, Lederberg discovered genetic recombination in bacteria in 1946, a major landmark in molecular biology. Scientist, administrator, statesman and philosopher, Lederberg was awarded the Nobel Prize for Physiology and Medicine in 1958 and the U.S. National Medal of Science in 1989.

Biomedical science, in contrast to physics, is bereft of a theoretical structure that can apply formal logistical procedures to codify the meaning of a precept, to demand a rigorous statement of boundary conditions for the application of a mathematical rule. We have common language, not algebraic formulae, as our everyday mode of discourse. The conceptual structures of our field are therefore particularly vulnerable to the crystallization of half-truths, even of puns, as the scaffolding, but also the constraints of our research.

In the discovery of the cholera exotoxin, S. N. De[3] then deserves our admiration at several levels. The nearly coincidental discovery in the 1880's of the cholera vibrio, on the one hand, and of the diphtheria toxin on the other, was followed by decades of productive research on toxins as the mediators of pathogenicity in a variety of diseases. But the paradigm failed for cholera. The truism "Toxins kill" had been translated into an experimental routine, "tested by intraperitoneal inoculation" which was simply inappropriate for this disease. De's clinical observation led him to the bold thought that dehydration was a sufficient cause of the pathology of cholera, that the cholera toxin might kill "merely" by stimulating the secretion of water into the bowel.

Another source of rigidity can also be traced to Koch's needful housecleaning of bacterial polymorphism[4], that bacteria are fixed species. We have still to uncover all of the subtleties of bacterial adaptation to their environments, but *Vibrio cholerae* may be unusually adept in amplifying specific DNA sequences in response to its local environment [5]. De had a good intuition about the need to use carefully selected and maintained strains in the demonstration of the exotoxin.

The ferocity of cholera as a pandemic disease may well have evoked passions that reinforced the "Killer" image of the vibrio; one source of postmaturity of discovery in microbiology may be the preeminence of workers who find it difficult to love, and thereby to understand an enemy which is such a scourge to mankind[6].

Our appreciation for De must then extend beyond the humanitarian consequences of his discovery. It is appalling to consider the millions of needless deaths that stem from the reign of "Toxins kill"; no less than those that flow from the still imperfect application of means of rehydration. But he is also an exemplar and inspiration for a boldness of challenge to the established wisdom, a style of thought that should be more aggressively taught by example as well as precept.

Many other examples can be found, though hardly any with the poignant consequences of the 70 year delay in cholera: bacteria (Schizomycetes) divide by fission; enzymes are proteins; mutations are always deleterious (in fact most are neutral) – these are some of the slogans that have been stepping stones, but later stumbling blocks in the progress of science. Can we but find a still deeper theoretical foundation for logical argument and expression in our arena of research [7]?

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2. Lederberg, Reflections on Scientific Biography in *Excitement and Fascination of Science*, Annual Reviews, Inc., Palo Alto, CA, 1990, Vol. III, pp. xvii–xxiv.
3. De, S. N., *Enterotoxicity of Bacteria-free Culture Filtrate of Vibrio cholerae*, *Nature*, 1959, **183**, 1533–1534.
4. Dubos, R. J., *The Bacterial Cell*, Harvard University Press, Cambridge, Mass., 1945.
5. Mekalanos, J. J., *Duplication and Amplification of Toxin Genes in Vibrio cholerae*, *Cell*, 1983, **35**, 253–263.
6. Zuckerman, H. A. and Lederberg, J., *Forty years of Genetic Recombination in Bacteria. Postnature Scientific Discovery?* *Nature*, 1986, **327**, 629–631.
7. Woodger, J. H., *The Axiomatic Method in Biology*, Cambridge University Press, Cambridge, 1937.

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Cholera Research – The Prelude

The third watershed, at the turn of the 1950s, marked the end of the long period of stagnation in interest in the disease, at any rate in the West. It culminated, fittingly, in the publication in 1959 of Pollitzer's comprehensive and conscientious monograph on cholera.

Pollitzer's monograph appeared just too soon to record the beginning of the new era of progress in the understanding of cholera, which is the object of the present history, however inadequately, to record. These beginnings were marked by the publication in the same year as the monograph, 75 years after Koch had postulated the existence of a cholera poison, of a report by S. N. De in Calcutta on the discovery of cholera toxin. And this discovery came in timely concatenation with new outbreaks of cholera beyond the borders of its homeland. In 1958, an epidemic of cholera in Bangkok attracted the interest of American investigators – an interest that had already been foreshadowed by the intervention of the U.S. Navy in an outbreak in Egypt in 1947. The Bangkok outbreak was the scientific, if not the bacteriological, curtain-raiser for the seventh cholera pandemic, which erupted in the Phillippines in 1961. This was the beginning of the invasion of a greater part of the world than had previously been affected by the cholera vibrio – not the classical *Vibrio cholerae*, but the hitherto largely ignored and apparently harmless biotype *Vibrio eltor*, which, though meeker, is in fact more sinister because it is more able to survive. By now, the Americans, though not themselves affected by the disease, had the will, and enough experience, to deal with it. Out of these beginnings there grew over the last two decades an immense effort of investigation in Dacca and Calcutta, and in the United States. It has resulted in an explosion of knowledge not only about the nature and the treatment of cholera, and of other even more serious because more wide-spread diarrhoeal diseases affecting countries all over the world, but also about the scientific principles that are fundamental to the normal as well as to the abnormal functioning of the animal organism.

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