



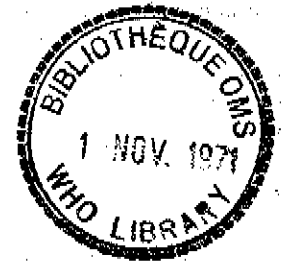
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EXPERIMENTAL MODELS OF ENTERIC INFECTIONS

by

Samuel B. Formal and Peter Gemski, Jr¹



The knowledge of "host-parasite" relationships acquired from experiments using animal laboratory models has contributed significantly to our present understanding of the pathogenesis of bacterial diseases of the human intestinal tract and of the immune mechanisms involved. The obvious, however, should be stated at the outset, namely that the principles derived from laboratory experiments must be applied with caution when they are extrapolated to problems of human disease processes. At best, laboratory models offer a convenient way to gain insight into possible disease mechanisms and thus enable one to formulate working hypotheses as to how these might play a role in natural diseases of man. In the final analysis, confirmation of any hypothesis must in some way be achieved in human beings.

Almost exclusively from findings derived from animal models, two mechanisms of how pathogenic enteric bacteria cause disease have been proposed. One, in which organisms of the genus *Shigella* are the classic example, involves the penetration of the intestinal epithelial cell by virulent bacteria. The bacteria then multiply in the intestinal mucosa causing a destruction of the epithelium, which results, in the most severe case, in characteristic ulcerative lesions of the large bowel and diarrhoea with blood and inflammatory cells in the stool (LaBrec et al., 1964; Voino-Yasenetsky & Khavkin, 1964; Ogawa et al., 1967).

Several laboratory models which may reflect an organism's ability to cause dysentery-like disease in man are available presently. Most, if not all, sub-human primates are natural hosts for dysentery bacilli and the disease, as it occurs in these animals, is similar clinically to that seen in man. In addition, both the distribution and the histological characteristics of the intestinal lesions in primates with shigellosis are typical of those observed in human beings (Gvazava, 1958). In such diseased animals, dysentery bacilli are observed both in the intestinal lumen and in the mucosa of the colon, while in infected non-symptomatic carriers the organism is observed only in the lumen of the bowel (Formal et al., 1966). Because of this similarity in host reaction, sub-human primates serve as the model of choice for study of the pathogenesis of bacillary dysentery and host immune mechanisms and for testing safety and potency of vaccines. The major disadvantages of using this model, however, are the cost and the possible endangerment of species due to over-exploitation.

¹ Walter Reed Army Institute of Research, Washington, D.C. 20012.

Other laboratory models that are perfectly acceptable for detecting the ability of a dysentery bacillus to penetrate the intestinal epithelium are available. These, therefore, can be effectively utilized to study the initial step of the disease and as an aid to formulate hypotheses prior to initiating experiments in primates. The models include the rabbit ileal loop technique (Orm et al., 1965; Yahagi, 1967), the starved, opiated guinea-pig (Formal et al., 1958) and the Sereney test (Sereney, 1957). The latter procedure - a simple, reliable test to perform and interpret - determines the organisms' capacity to produce keratocojunctivitis after invading the corneal epithelium of either the rabbit or the guinea-pig. Pathogenicity data obtained from these laboratory models correlate with findings obtained in sub-human primates and, to the extent that they have been examined, with findings in human beings.

A second known mechanism by which enteric bacteria cause disease in man, again almost exclusively elucidated by animal models, is exemplified best by infections with Vibrio cholerae. Unlike the situation seen in classical bacillary dysentery, the major site of V. cholerae multiplication is in the lumen of the small intestine. In the most severe form of cholera, large amounts of fluid are lost from the small intestine by the action of an enterotoxin elaborated by the organism on the epithelial layer of the mucosa. The intestinal epithelium remains intact, however, throughout the disease. Several animal models have been utilized to accumulate this information. Live cholera vibrios will cause fluid loss into the intestine and/or death when used in the ligated rabbit ileum (De & Chatterje, 1953), the infant rabbit (Dutta & Habbu, 1955), the starved opiated guinea-pig, (LaBrec et al., 1965) or the adult dog models (Sack & Carpenter, 1969). With the exception of the late stages of the rabbit ileal loop infection, fluid enters the lumen through an intact epithelium in all of these models. The composition of the fluid and the microscopic anatomy of the mucosa in these experimental systems are similar to those seen in the disease of man. Besides employing live cells, cell-free material can be prepared from V. cholerae in a highly purified form which causes fluid to be lost into the intestinal lumen of animal models and, as far as can be determined, mimics the infection itself. In addition, the enterotoxin molecule (or molecules very closely associated with it) also possesses the ability to alter the vascular permeability of the skin of rabbits or guinea-pigs. This finding provides a convenient technique to test for toxin activity and to determine antitoxin levels in biological material (Craig, 1965, 1970).

All of the laboratory models described here are used to assess two important characteristics of potentially pathogenic enteric bacteria: the ability to penetrate and multiply in the intestinal mucosa or the capacity to produce a toxin capable of causing fluid loss in the lumen of the bowel. They can therefore be utilized in the laboratory to study the characteristics of organisms other than dysentery bacilli and V. cholerae, and indeed strains of E. coli have been described which possess the characteristics of either Shigellae or V. cholerae. The reliability of such models for studying E. coli pathogenesis has been confirmed in man (Dupont et al., 1971).

While some basic questions concerning the pathogenesis of enteric infections appear to have been answered, more have arisen (as one might expect). Two important problems which must be solved are the mechanism of epithelial cell penetration of dysentery-like organisms and the mode(s) of action of enterotoxin. Laboratory models will play a major part in the solution of these questions, as attested by the progress being made in research on the mode of action of enterotoxin. In closing, one should re-emphasize that the results obtained from such animal models can serve only as a starting point in the study of diseases of man, by providing a foundation for intelligent investigations in man. Oftentimes we are led down paths of confusion when this note of caution is unheeded.

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