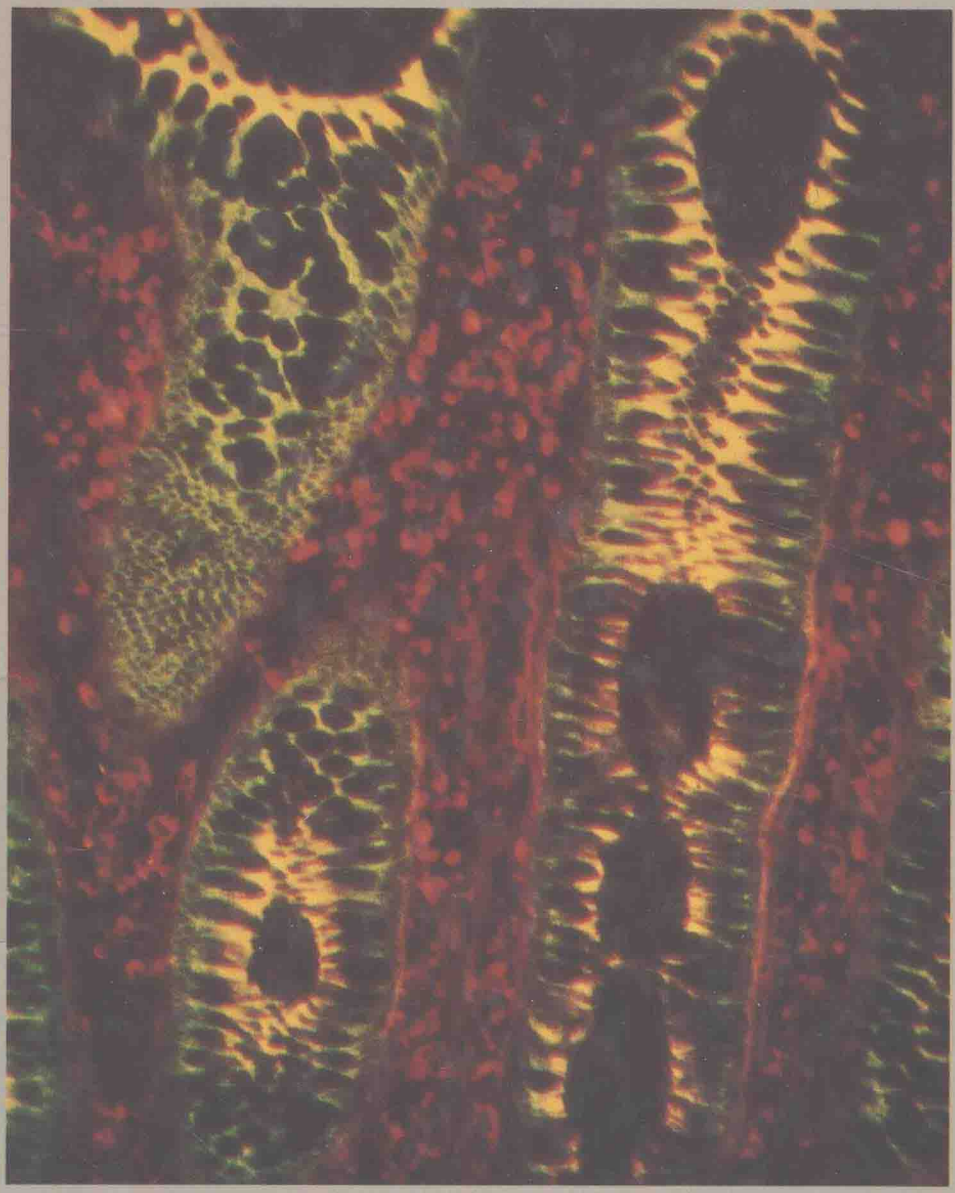
Development of Vaccines and Drugs against Diarrhea



Editors: Jan Holmgren Alf Lindberg Roland Möllby

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11th Nobel Conference, Stockholm 1985

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Jan Holmgren Alf Lindberg
Roland Möllby

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Cover picture.
Paired immunofluorescence staining for IgA (*red*) and secretory component (SC) (*green*) in section of colonic mucosa shows IgA-producing immunocytes in lamina propria and epithelial uptake of IgA. Mixed colour (*yellow*) signifies combination of IgA and SC; note green patchy fluorescence adjacent to nuclei of epithelial cells indicating accumulation of free SC in the Golgi zones. The mucin of Goblet cells is negative.

(Courtesy of Dr P. BRANDTZAEG, Oslo, Norway)

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Session 5. Travelers' diarrhea

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PREFACE

The Nobel Conference "Recent Advances in Vaccines and Drugs Against Diarrhoeal Diseases" was held in Stockholm in June 1985. It was, in fact, the 3rd international meeting on diarrhoeal disease research organized by Swedish scientists in collaboration with The World Health Organization. The first meeting was the Nobel Symposium on "Cholera and Related Diarrheas", held in 1978. This was followed in 1980 by the Nobel Conference "Acute Enteric Infections in Children. New Prospects for Treatment and Prevention".

During the past 10 years rapid progress has been made in our knowledge about diarrhoeal disease. It is important that workers in this area always keep in mind their responsibility that new discoveries be applied, especially in the developing countries where enteric infections and diarrhoeal disease continue to be a leading health problem. It is our hope that the lectures and discussions held during the Conference and published in this volume will help to assure the rapid transfer of new knowledge into the development of prophylactic and therapeutic measures against diarrhoeal diseases.

Members of the organizing committee for the 1985 Conference were Tord Holme, Jan Holmgren, Alf A. Lindberg, Michael H. Merson, Roland Möllby and Sune Bergström. The Conference was sponsored by the Marcus Wallenberg Foundation for International Cooperation in Science, the World Health Organization, the Nobel Assembly of the Karolinska Institute and the National Bacteriological Laboratory. The members of the organizing committee would like to express their sincere thanks to the sponsors of the Conference.

For the Organizing Committee,

Tord Holme

INTRODUCTORY OVERVIEW

Development of Vaccines and Drugs against Diarrhea. 11th Nobel Conf., Stockholm 1985, pp 9–22. (Eds. J.Holmgren, A.Lindberg & R.Möllby.) Studentlitteratur, Lund, Sweden 1986.

Immune mechanisms in enteric infections

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We describe the immunological and nonimmunological components of the first and second lines of defence of the gut against enteric infections, and discuss the prospects for reinforcement of this defence system by vaccination. The secretory IgA (SIgA) system is described in detail with special emphasis on synergism between antibacterial and antitoxic SIgA antibodies in protection against disease caused by enterotoxigenic pathogens, and on long-lasting immunologic memory in this system. We also draw attention to recent findings that might suggest an interplay between gut immunology, the local nervous system and gut epithelial cell physiology.

*

Enteric infections associated with diarrhoeal disease may be caused by many different bacteria, viruses and parasites. The gut has a complex system of immunological and nonimmunological host defence factors. Their function is to protect the body against harmful effects from various enteric pathogens and their toxins as well as from uptake of potentially allergy–inducing food antigens and from tissue destroying effects of the host's own proteolytic enzymes. In this short overview these factors and their action are described with the purpose to provide a background to the more specific vaccine-related topics that will be discussed in subsequent papers. In addition, this article draws attention to some new findings suggesting intriguing interactions between gut immunology, the nervous system and epithelial cell physiology. These concepts are as yet highly

speculative, but could have a profound relevance for the overall understanding of intestinal function and thereby be central to the main theme of this conference, *i.e.* the development of effective vaccines and drugs for the control of diarrhoeal disease.

First and second lines of defence

At the risk of grossly oversimplifying very complex matters we will distinguish between what we call the first and second lines of defence of the gut, and their different roles in relation to protection against enteric infections.

The first line of defence consists of a battery of nonimmunological and immunological factors in the gut lumen, in the mucus layer and on the epithelial surface (Table 1). These factors usually comprise an effective mucosal barrier against both noninvasive and invasive organisms thus preventing infection and development of disease. The immunologically specific components of this system, when being reinforced by the development of an immune response during the course of infection, also appear to be the major factors limiting the duration of the natural disease. However, this latter role would essentially be limited to noninvasive infections and organisms, such as cholera, enterotoxigenic *E. coli* diarrhoea and giardiasis.

Recovery from diseases with invasive organisms such as shigellae, salmonellae and, possibly, rotavirus on the other hand would primarily depend on development of effective deeper tissue immunity. This second line of defence, which might also play some role in preventing the development of disease with tissue invasive organisms contains almost the full set of systemic and deep mucosal immune factors: serum-derived antibodies operating in conjunction with the complement system and phagocytotic cells, and of special importance in relation to many of these infections various cells with capacity for cell-mediated immune reactions. These might include MHC-restricted T cell cytotoxicity, T cell enhanced macrophage functions, antibody dependant cell-mediated cytotoxicity (ADCC), and natural killer (NK) cell activities (Table 1).

Non-immunological mucosal barrier

Returning to the first line of defence the most important non-immunological intraluminal factors are the gastric acidity, proteolytic enzymes and peristalsis.

On the mucosal surface the mucus coat consists of a highly viscous gel of crosslinked glycoproteins. This gel is a physical barrier against mucosal attack by most ingested microorganisms. It may also function as a chemical trap for pathogens by containing receptor-like carbohydrate moities which can catch organisms and toxins before they reach the epithelial target cells.

The composition of the intestinal microvillus membrane, finally, determines whether mucus-penetrating bacteria, toxins or viruses will bind to the epithelial cells. The membrane composition differs between species. It also changes as the epithelial cell migrates up the villus, with age, and with blood group. These differences could be important in explaining species, age or blood group related differences in susceptibility