CHAPTER 1

Introduction

R. Fuller

1.1 DEVELOPMENT OF COMMERCIAL PREPARATIONS

The history of the probiotic effect has been well documented many times previously (see e.g. Bibel, 1982; Fuller, 1992). The consumption of fermented milks dates from pre-biblical times but the probiotic concept was born at the end of the last century with the work of Metchnikoff at the Pasteur Institute in Paris.

In the century that has elapsed since Metchnikoff's work, the probiotic concept has been accepted by scientists and consumers throughout the world. Attempts to refine the practice from the use of traditional soured milks to preparations containing specific microorganisms have occupied the thoughts and endeavours of scientists in many different countries. But, in spite of the large amount of effort expended in attempting to explain and define the effect, it has to be admitted that little is known of the way in which probiotics operate.

There are likely to be several different mechanisms because it seems highly improbable that a mode of action that explains resistance to microbial infection will also hold true for improved milk production or alleviation of lactose malabsorption.

The lack of fundamental knowledge about the mechanism of the probiotic effect has not deterred the development of a great many probiotic preparations destined for treatment of various conditions in man and animals. There are currently over 20 products on the market in the UK. The dearth of basic information about the probiotic effect has meant that much of the development has been empirical and not always based on sound scientific principles. One factor that has been used in the selection of probiotic cultures has been the ability to adhere to gut epithelial cells of the animal to which the probiotic is being fed.


CHAPTER 3

Antibiotic-associated diarrhoea: treatments by living organisms given by the oral route (probiotics)

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3.1 INTRODUCTION

Pseudomembranous colitis and a large percentage (about 30%) of antibiotic-associated diarrhoea are caused by the overgrowth of *Clostridium difficile* in the human digestive tract. This overgrowth is mainly due to disorders in gut bacterial populations leading to disruption of the colonization resistance to pathogens (Hentges, 1992). *C. difficile* produces two toxins (an enterotoxin and a cytotoxin) which are responsible for the disease (Figure 3.1). Medical treatments mostly involve antibiotics (vancomycin or metronidazole) that do not facilitate the restoration of the colonization resistance, so that relapses are often observed. The aim of this chapter is to overview *C. difficile*-associated enteropathies as well as bacterial toxins and to present the current and future applications of probiotic treatments in a preventive or curative mode.

3.2 ANTIBIOTIC-ASSOCIATED DIARRHOEA AND PSEUDOMEMBRANOUS COLITIS

This subject has been reviewed by different authors (among them Bartlett, 1979, 1994; Lyerly, Krivian and Wilkins, 1988; and Rolfe and
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Disorders in autochtonous microflora

C. difficile overgrowth

Toxin A
Toxin B

Gut lumen
Enterocyte

Fig. 3.1 General outline of pathology due to Clostridium difficile. 1, attachment to brush border receptor (R); 2, enterotoxicity and cell death; 3, inflammation process and dissemination of both toxins (A and B) in systemic circulation.

Finegold, 1988, in a book containing 16 reviews on the subject). In order to reduce the number of cited references, only the studies not mentioned in these reviews will be cited here.

At any age of life composition of the intestinal microflora represents a fragile equilibrium between different bacterial populations which can be predominant, subdominant or transitory. The global functions of the microflora depend on this quantitative and qualitative equilibrium. Antibiotic treatments induce a complete or partial destruction of the intestinal microflora. At the end of the treatment, bacteria hidden in niches, in the environment or provided by food colonize the gut. However, the initial equilibrium involved in crucial functions such as colonization resistance to pathogen bacteria is not easily restored (Hentges, 1992).

Antibiotic treatments often lead to antibiotic-associated diarrhoea, the extreme form of which is pseudomembranous colitis. Antibiotic-associated colitis was recognized (Bartlett, 1979) as 'an intriguing paradox of medical progress that compromises the therapeutic utility of an important group of antibiotics, adds a potential obstacle to new drug development and challenges our ability to fashion the welter of clinical and pathologic observations into a cohesive disease entity'.

3.2.1 The pathological effects

An antibiotic-associated diarrhoea generally occurs following several days of antibiotic treatment but it can also be observed at the end of the treatment or during the following 6 weeks. The severity of diarrhoea can range from a mild increase in stool frequency, sometimes associated with an abdominal pain and fever, to debilitating diarrhoea.