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## Genetic aspects of monoclonal gammopathy

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INTRODUCTION

Traditionally, research in diseases associated with a monoclonal component is one of the scientific interests on the Department of Internal Medicine, University Hospital Groningen, The Netherlands. The study reported in this thesis and performed in the Immunochemical Laboratory, is to be regarded as a continuation of this research-line.

The etiology of a monoclonal gammopathy is still an open question. Reported multiple occurrence of monoclonal components and other immunoglobulin abnormalities within families suggested the influence of genetically determined factors. In order to trace such factors Festen started in 1970 a systematic study of family members of patients with myelomatosis, one of the clinical entities associated with an M-component. In 1974 in his thesis Festen reported on serum immunoglobulin levels in first-degree relatives of patients with myelomatosis. The serum immunoglobulin levels being regarded as a reflection of the genetically controlled magnitude of immune responsiveness.

In the present thesis research has been focussed on two additional genetically determined factors, which could play a recognizable role in the onset of monoclonal gammopathy. In an extension of the family study the influence of a disturbance in the genetic control of the heterogeneity of an immune response has been studied in three families with multiple occurrence of M-components. The second factor studied in this thesis is the genetic control of immunoglobulin structure. A patient with two M-components in his serum was investigated in terms of the relationship in structure and cellular localization of biosynthesis of both monoclonal proteins.

The complexity and the many aspects of the present study gave rise to a detailed chapter 2. The structure of the immunoglobulin molecule is reviewed. Special attention is payed on idiotypy because antisera raised against idiotypic determinants of M-components form an important experimental tool in this study. The genetic control of the immune response is ample discussed. Data on the genetic control of immunoglobulin structure are summarized in view of the experiments on double gammopathy (reported in chapter 4). The genetic control of the magnitude of the immune response is discussed in relation to the family study which preceded the present one. The genetic control of the heterogeneity of an immune

response is reviewed because the hypothesis tested in our part of the family study is mainly based on these data (reported in chapter 3). B-cell proliferative diseases are briefly mentioned in order to stress their close relationship. Finally, a survey is given on the familial occurrence of immunoglobulin abnormalities and on double gammopathy.

The experimental data are comprised in two chapters. In chapter 3 our hypothesis that an inherited restriction in the number of available V-region genes contributes to a genetic predisposition for monoclonal gammopathy is tested. Results are shown and discussed of experiments performed with a hemagglutination inhibition technique and with a radiobinding inhibition assay. In chapter 4 results are described of a study on a patient with double gammopathy. Idiotypic antisera, raised against the distinctive M-components were applied in radioimmunoassays and in immunofluorescence studies of bone marrow smears.

In chapter 5 the experimental data from chapter 3 and 4 are discussed with regard to their contribution to the understanding of the genetics of the immune response. Finally, a summary is given in English and Dutch, followed by a list of references.