SUMMARY AND CONCLUSIONS

The clinical significance of Raynaud's phenomenon (RP), an intermittent vasospasm of the digital arteries on exposure to cold, has a considerable variability. It may be a harmless, isolated vascular spasm, more or less hindering the patient's daily life, or it may exist for several years as the first and only symptom of a sometimes fatal, autoimmune connective tissue disease (CTD) like scleroderma and systemic lupus erythematosus (1). To distinguish these two courses of RP in a patient, the phenomenon has to be followed for twenty years before it may be considered as harmless (2).

The question underlying this thesis was: can we predict, with the aid of immunological studies, whether or not RP will develop into one of the above mentioned CTD? The expectation, that clinical immunology might contribute to an earlier diagnosis of CTD in RP, stems from the experimental immunology, which demonstrated quantificable immunological impairments prior to the onset of clinical disease (3). Immune complexes (IC) were studied because they are considered to play a pathogenetic role in autoimmune CTD. Hence the finding of an increased amount of IC in patients with RP might be an indication for the CTD-associated form of RP. The presence of ANA was studied with a new immunofluorescence technique, which is possibly more specific for the diagnosis of autoimmune CTD. Potentially existing imbalance between cell-mediated and humoral immunity was investigated because this imbalance can be demonstrated in the experimental model in an early stage. Finally the question was asked whether or not a genetic predisposition exists for the occurrence of these CTD.

Summary of the results

The method to objectify the severity and the classification of the phenomenon are discussed in the first chapter. The significance of the finding of elevated numbers of phagocytosed IC in polymorphonuclear leucocytes of patients with RP is discussed in the second chapter. A distinct correlation existed between the severity of the phenomenon and the level of IC, a less distinct correlation existed between IC and the classification of RP. The experiences with a newly developed immunofluorescence technique for the detection of ANA are reported in the third chapter. In this technique human fibroblast monolayers are applied as nuclear substrate. The advantages of this substrate are: simpler performance of serumtitrations and better recognition of the different nu-

clear fluorescence patterns, which permit a more exact determination of the antibody specificity with regard to the antigens involved. This method is as sensitive as other immunofluorescence techniques, but probably more specific for the diagnosis of CTD. This latter was concluded from the finding of high titres of fibroblast associated ANA in patients with RP and symptoms of a CTD.

The imbalance between cell-mediated and humoral immunity was investigated. The results of this study are described in the fourth chapter. Cell-mediated immunity was studied by means of in vitro lymphocyte stimulation with plant mitogens PHA and Con A. An impaired lymphocyte response to low concentrations of Con A was demonstrated in all patients with RP. Furthermore, it was found that the response to Con A was most depressed when elevated serum immunoglobulin levels were present. To what extent this combination of impaired Con A response and elevated immunoglobulin levels represents the expected imbalance between cell-mediated and humoral immunity can only be answered by a follow-up study.

To investigate the possibility of a genetic predisposition for autoimmune CTD, the distribution of 24 histocompatibility antigens (HLA) in patients with RP was compared with the distribution of HLA in the Netherlands (4). The patients with RP had a significant increase of HLA-A2. A difference in distribution, which was not statistically significant, was found between the patients with RP and CTD and the patients with RP without CTD. However, a significant difference did exist between the RP with CTD and RP without CTD groups in distribution of HLA-B8. Patients with RP and HLA-B8 run a greater risk to develop a CTD than those without HLA-B8.

Conclusions

The results of the immunological studies described in this thesis, demonstrate distinct immunological disorders in many patients with RP prior to the diagnosis of the CTD scleroderma and systemic lupus erythematosus. How far these disorders, when present in patients with isolated RP will contribute to the development of a CTD in this group has to be proven by a follow-up study. However, cluster analysis revealed that immunological disorders correlate with certain characteristics of RP. The presence of increased numbers of IC indicates more severe vascular spasm, the presence of ANA indicates a systemic disease, an impaired lymphocyte response to Con A is more pronounced

in RP with increased serum immunoglobulin levels, and the presence of HLA-B8 is a risk factor for the development of scleroderma or systemic lupus erythematosus. To what extent the absence of these immunological phenomena quarantees the patient to have an annoying but not dangerous vascular spasm, can only be said after a follow-up period of several years.

References

1. Bennett, R., Bluestone, R., Holt, P.J.L. and Bywaters, E.G.L. (1971) Survival in scleroderma. Ann. rheum. Dis. 30, 581.

2. Blain III, A., Coller, F.A., Carver, C.B. and Arbor, A. (1951) Raynaud's disease. A study of criteria for prognosis. Surgery 29, 387.

3. Talal, N. (1977) Autoimmunity. Genetic, immunologic, virologic and clinical aspects. Academic Press, New York 1977, p. 188, p. 556.

4. D'Amoro, J. (1978) HLA polymorphisms in the Netherlands. A study in population- and immunogenetics. Thesis, Leiden.