

van der Meer J B. Granular deposits of immunoglobulins in the skin of patients with dermatitis herpetiformis. An immunofluorescent study.

Brit. J. Dermatol. 81:493-503, 1969.

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In 10 of 12 patients with dermatitis herpetiformis (DH), granular deposits of immunoglobulins (Ig) were demonstrated in the basement membrane zone of uninvolved skin using direct immunofluorescence; in contrast, pemphigoid (Pd) control patients showed a linear immunofluorescence staining pattern. These findings in DH could be explained by the predominance of IgA in the skin in DH, in contrast to IgG in Pd. [The SC⁷® indicates that this paper has been cited in over 150 publications.]

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In 1966 when I began my study of dermatology in Utrecht, Leo Jansen, head of the Department of Dermatology, asked me to participate in laboratory investigations. I came to work with Rudi H. Cormane, who aroused my interest in immunodermatology and introduced me to the principles of the immunofluorescence (IF) technique, which was a new item in dermatology in those days.

Soon my interest focused on dermatitis herpetiformis (DH). My own results from a pilot study revealed positive findings, but results of IF studies in DH were conflicting. In a study in 1967 Cormane reported unspecified *in vivo* binding of immunoglobulins (Ig) in the skin in DH.¹ However, since he demonstrated concomitant albumin binding as well, Cormane considered this an aspecific finding, and he agreed with the results of other authors who never demonstrated significant IF findings in DH.

Cormane left Utrecht to become a professor of dermatology in Amsterdam and advised me to stop further investigations on DH. I persisted in my studies, however, and with the skillful technical assistance of Jose Nefkens I focused first on extensive specification studies on a va-

riety of conjugates and antisera before using them in further IF studies. I knew that the IF results in the literature were based on the use of monospecific antihuman IgG conjugates. In a screening study on the skin of 10 DH patients, I used a well-specified polyspecific antihuman Ig conjugate that reacted with IgA and IgM as well as IgG. This resulted in the *Citation Classic*. Obtaining monospecific antihuman IgA conjugate was very difficult in those days. With the aid of Bert Feltkamp (presently professor of clinical immunology in Amsterdam), Rudi Ballieux (professor of clinical immunology in Utrecht), and many other people, I eventually obtained a set of monospecific antisera and conjugates to human IgG, IgA, and IgM, respectively, to continue my studies, which culminated in a thesis.²

The main interest of the granular IgA deposits, of course, is not only their diagnostic significance, but also their meaning in the etiology and pathogenesis of the disease. According to a working hypothesis,² the gluten-induced gut pathology facilitates the entry of still-unknown antigens, forming immune complexes together with the IgA-class antibodies, which eventually deposit in the skin. This hypothesis still appears to be relevant at present, as shown from further studies on the absence of gluten in the DH skin^{3,4} and the rapid improvement of DH skin lesions after elemental diet.^{5,6} Contrary to the opinion of L. Fry and coworkers,⁷ these results argue against a direct relationship of the DH skin lesions with gluten and point instead to other harmful dietary substances as causes of the DH skin rash.

This paper has been frequently cited probably because of its diagnostic significance. J.O'D. Alexander discussed the findings reported in the *Citation Classic* as well as those in my thesis.⁸

As to awards and honors, it may be of interest that in the past six years I have been asked twice, on different occasions, to become professor of dermatology at university hospitals in The Netherlands. (I refused for personal reasons.)

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7. Fry L, Leonard J N & Griffiths C E M. Letter to editor. (The cause of dermatitis herpetiformis.) *Arch. Dermatol.* 123:293, 1987.
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