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DIE MEGANISMES VERANTWOORDELIK VIR HASHIMOTO SE SIEKTE, EN VERWANTE AANGELEENTHEDE

Die ontdekking van verhoogde gammaglobuliene en abnormale serum-proteïen-uitvlokkingtoetse by Hashimoto se siekte,* hul geleidelike terugkeer na normaal, ná die verwydering van die kropgeswel,[1-3] en die infiltrasie van die tiroïed deur selle wat ons weet teenliggaampies vervaardig, het Roitt en sy medewerkers laat postuleer dat hierdie veranderings veroorsaak word deur 'n immuniseringproses wat teen die skildklier gerig is. Hulle het toe aangetoon dat die bloedwei van pasiënte met hierdie soort kropgeswel presipiterende teenliggaampies teen menslike tiroglobulien bevat.

Die teenliggaampies is blykbaar spesifiek teen tiroglobulien gerig, want negatiewe uitslae is met ekstrakte van ander menslike weefsels behaal. Die presipitiene was aantoonbaar wanneer ongesuiwerde skildklierekstrakte uit normale en vergiftigende kliere gebruik was en dié het 'n beperkte spesie-spesifisiteit getoon. Ná die fraksioneer van die pasiënte se serum deur sone-elektroforese op sellulose-kolomme en deur immuun-elektroforese, is dit bevind dat dit die gammaglobulien was wat die presipiterende teenligaampies bevat.

Roitt en Doniach[5] het die bloedwei van 107 lyers aan Hashimoto se siekte ondersoek. Sewentig van hulle was glad nie behandel nie, of slegs met tiroïedhormoon behandel, en by 52 van hulle was die presipitientoetse positief. Op een na het die 18 negatiewes positief gereageer toe hulle deur komplement-fiksering getoets is—ekstrakte van 'n tirotoksiese klier is as antigeen gebruik. Die serum van die pasiënt wat negatief op beide toetse gereageer het, is vervolgens deur 'n meer sensitiewe presipitienmetode bestudeer, en daar is bewys dat dit wel 'n sekere hoeveelheid teenstof bevat het, hoewel minder as die ander. Uit die 37 ná-operatiewe Hashimoto-serums, het slegs 14 positiewe presipitientoetse gelewer, en dit is bevind dat die voorkomssyfer van negatiewe uitslae toeneem namate groter gedeeltes van die skildklierweefsel verwyder word en namate 'n langer tydperk na die operasie verstryk. Roitt het voorts die serums van 238 pasiënte met ander skildkliersiektes deur middel van die presipitientoets ondersoek. Nie een van die pasiënte met skildkliervergiftiging of nie-toksiese nodulêre krop het enige presipitien in hul serums getoon nie. Verbasend genoeg het 6 uit 33 pasiënte met primêre miksedeem, en

* Hashimoto se siekte is in verlede week se uitgawe van hierdie *Tydskrif* (bl. 395) deur die redaksie bespreek.

EDITORIAL

MECHANISMS RESPONSIBLE FOR HASHIMOTO'S DISEASE, AND RELATED CONSIDERATIONS

The finding of raised gamma globulins and abnormal serum-protein flocculation tests in Hashimoto's disease,* their gradual return to normal after the removal of the goitre,[1-3] and the infiltration of the thyroid gland by cells known to produce antibody, led Roitt and his co-workers to postulate that these changes were caused by an immune process directed against the thyroid. They then demonstrated that the sera of patients with this type of goitre contained precipitating antibodies against human thyroglobulin.

The antibody was apparently specifically directed against thyroglobulin, since negative results were obtained against extracts of other human tissues. The precipitins were demonstrable when crude thyroid extracts from normal or thyrotoxic glands were used, and these showed a narrow species specificity. After fractionation of patients' serum by zone electrophoresis on cellulose columns and by immuno-electrophoresis, it was found that the precipitating antibody was contained in the gamma globulin.

Roitt and Doniach[5] examined sera from 107 patients with Hashimoto's disease. Seventy of these were untreated or treated with thyroid hormone only and 52 of them gave positive precipitin tests. All but one of the 18 negative ones gave positive results when tested by complement fixation, extracts of thyrotoxic gland being used as antigen. The one serum which was negative to both tests was then further studied by a more sensitive precipitin method and shown to contain some antibody, though less than the others. Of 37 post-operative Hashimoto sera, only 14 gave positive precipitin tests, and the incidence of negative results was found to increase with the amount of thyroid tissue removed and with the length of time elapsed since the operation. Roitt proceeded to examine the sera of 238 patients with other thyroid diseases by the precipitin test. No patients with thyrotoxicosis or non-toxic nodular goitre had any precipitins in their sera. Surprisingly, 6 patients with primary myxoedema out of 33, and 4 with subacute thyroiditis, also gave quite strong precipitin tests.

* Hashimoto's disease was the subject of an editorial in last week's issue of this *Journal* (page 395).

4 met subakute skildklierontsteking ook taamlike sterk presipitientoetse gelewer.

Die aantoon by die chroniese skildklierontsteking van Hashimoto van teenliggaampies in omloop, wat teen die pasiënt se eie skildklier werk, en die bevestigde selvergiftigende uitwerking van eksperimenteel verkrygde outo-immunisering, het daarop gedui dat die siekte moontlik deur 'n self-voortsettende vernietigingsproses ontstaan wat afhang van 'n immuunreaksie teen tiroglobulien of die een of ander proteïen in die skildklier. Roitt wys daarop dat aangesien tiroglobulien gewoonlik tot die follikels beperk is en nie vry sirkuleer nie, indiwidue nie gewoonweg 'n immunologiese verdraagsaamheid daartoe sal ontwikkel nie.

In hierdie verband het Witebsky en Rose[6,7] daarin geslaag om verskeie dieresoorte teen ekstrakte van soortgelyke skildkliere te immuniseer en het letsels in die skildkliere van sodanig behandelde diere waargeneem wat in baie opsigte ooreenstem met chroniese skildklierontsteking by die mens. Ons kan dus aanneem dat, by die mens, 'n uitstorting van tiroglobulien uit die follikel 'n reaksie van outo-immunisering kan uitlok en die indring van limfatiese selle tot die klier kan stimuleer, met gevolglike plaaslike vorming van teenliggaampies; die aangrensende follikels word sodoende beskadig en stel dan nog meer kolloïed vry. Met verloop van tyd kan die aantasting van die skildklier versprei, en afgeleë dele van die retikulo-endoteelstelsel kan by die produseer van teenliggaampies betrokke raak. Die klassieke geval van Hashimoto se siekte is 'n gevorderde en uiterste voorbeeld van hierdie proses.

Die ontdekking van presipitiene in die serum van pasiënte met primêre miksedeem sonder kropgewas, suggereer dat sommige gevalle van miksedeem 'n ander kliniese gevolg van dieselfde immunologiese proses kan wees. By die soort miksedeem wat ons by die Hashimoto-siekte teëkom, ontdek ons 'n fibrotiese klier met limfsel-infiltrasie. Histologies is hierdie twee kondisies merkwaardig eners—die verskil is dat daar by die een 'n kropgewas, en by die ander 'n abnormaal klein klier gevind word. Roitt meld dat die ontwikkeling van 'n kropgewas as gevolg van tiroïede self-immunisering moontlik op die vermoë van die klier om op TSH te reageer, berus.

Trotter,[8] wat die komplement-fikseringtoetse op hierdie probleem toegepas het, het teenliggaampies ook by 'n aantal pasiënte met skildkliervergiftiging aangetref. Hy vestig die aandag daarop dat kolle van limfweefselagtige selverandering in sommige kropgeswelle aangetref word en stel dus voor dat daar moontlik 'n verband bestaan tussen hierdie verandering en die aanwesigheid van komplement-fikserende teenliggaampies. Die navorsing wat tans gedoen word, kan dus die geleentheid bied om iets te leer oor die meganismes betrokke by Hashimoto se skildklierontsteking sowel as by primêre skildkliervergiftiging.

White[9] het die setel van die betrokke antigeen deur middel van die gloeigas-metode vir teenliggaampies ondersoek. Hy het bevind dat die antigeen, wat die Hashimoto-teenliggaampie lokaliseer, teenwoordig is binne die follikels, in die selle van die follikel-epiteel, en ook buitekant die follikels, in en rondom die infiltrerende limfselle.

Dit blyk dus dat die antigeen vryelik uit die follikels vloei, en dit is dus begryplik dat teenliggaampies gevolglik gevorm kan word. White het verder die aangrensende limfknope ondersoek en ontdek dat die periferale limfholtes

The demonstration of circulating antibodies against the patient's own thyroid gland in the chronic thyroiditis of Hashimoto, and the known cytotoxic effects of experimentally induced auto-immunization, suggested that the disease might arise by a self-perpetuating destructive process depending upon an immune response to thyroglobulin or some other protein in the thyroid gland. Roitt points out that since thyroglobulin is normally confined in the follicles and does not circulate freely, individuals will not normally acquire an immunological tolerance to it.

In this connection Witebsky and Rose[6,7] succeeded in immunizing several animal species against extracts of homologous thyroid glands and observed lesions in the thyroids of animals so treated which have many features in common with human chronic thyroiditis. Thus we may suppose that in the human subject a release of thyroglobulin from the follicle might elicit an auto-immune response and stimulate invasion of the gland by lymphoid cells with local antibody production, so causing damage to adjacent follicles with further release of colloid. In time the thyroid gland might become diffusely involved, and distant parts of the reticulo-endothelial system might be implicated in the production of antibodies. Classical Hashimoto's disease represents a late and extreme example of this process.

The finding of precipitins in the sera of patients with primary myxoedema without goitre suggests that some cases of myxoedema may represent another clinical result of the same immunological process. In myxoedema as in Hashimoto's disease we find a fibrotic gland with lymphoid infiltration. Histologically these two conditions are remarkably similar—except that in one there is a goitre and in the other a smaller than normal gland. Roitt remarks that the development of a goitre as a result of thyroid auto-immunity may depend on the ability of the gland to respond to TSH.

Trotter,[8] who applied the complement-fixation tests to the problem, found antibodies also in a number of patients with thyrotoxicosis. He points out that patchy lymphadenoid change is seen in some toxic goitres and hence suggests that there may be a correlation between this change and the presence of complement-fixing antibodies. Thus the present work may provide an opportunity for learning something of the mechanisms involved not only in Hashimoto's thyroiditis, but also in primary myxoedema and in primary thyrotoxicosis.

White[9] has investigated the localization of the antigen concerned by fluorescent antibody technique. He found that the antigen which localized the Hashimoto antibody was present within the follicles, in the cells of the follicular epithelium, and also outside the follicles, in and among the infiltrating lymphoid cells. Thus the antigen appears freely to pass out of the follicles, and it is easy to see that antibody formation might then result. White further examined the adjacent lymph nodes and found that the peripheral lymph sinuses of the nodes were crowded with large reticulo-

van die knope propvol groot retikulo-endoteelselle was wat sitoplasmiese ronde korreltjies van teenliggaampies bevat. Die antigeen bereik dus vermoedelik die limfknope langs die limfvate en vorm presipitiene met die teenliggaampie van die limf, wat dan opgeneem word deur die sinus-voeringfagosiete.

Die meganismes verantwoordelik vir die ontstaan van 'n obskure siekte is dus, binne die bestek van 'n baie kort tydjie, grotendeels toegelig en die bevindings klop op alle punte. Bowendien word ons gedwing tot die besef dat die siekte betreklik dikwels voorkom, en dat dit nou met heelwat sekerheid gediagnoseer en wetenskaplik behandel kan word. Die betrokke meganisme—een van outo-immunisering teen 'n antigeen spesifiek op 'n besondere orgaan gerig—hoewel maar pas ontdek, kan moontlik buite die enge bestek van Hashimoto se siekte van toepassing wees.

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8. Trotter, W. R., Belyavin, G. en Waddams, A. (1957): Proc. Roy. Soc. Med., **50**, 961.
9. White, R. G. (1957): *Ibid.*, **50**, 953.

endothelial cells containing cytoplasmic spherical granules of antibody. The antigen thus presumably reaches the lymph nodes *via* the lymphatics and forms precipitins with the antibody of the lymph, which are then taken up by the sinus-lining phagocytes.

In a very short time, then, the mechanisms responsible for the production of an obscure disease have been largely elucidated and the findings fit together at all points. Furthermore we have been made to realize that the condition is relatively common, and may now be diagnosed with considerable certainty and treated on a scientific basis. The mechanism responsible—one of auto-immunization against an organ-specific antigen—, though newly recognized, is one which may have application beyond the narrow field of Hashimoto's disease.

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