THE ROLE OF ALLERGY IN THE AETIOLOGY OF UVEITIS

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The purpose of this communication is to examine and analyse the role played by allergy in the aetiology of uveitis, with particular reference to endogenous anterior uveitis.

One defines allergy as 'the changed capacity of an individual to react to a foreign substance', and the disease is based on an antigen-antibody reaction causing hypersensitivity, usually to a bacteria or its soluble products or a foreign protein; moreover, the protein need not be foreign for an individual may react to one of his own proteins and this is called 'auto-immune disease'. Immediate and delayed reactions are recognized and both types can be demonstrated in uveitis.

The postulate that anterior uveitis is due to an immunopathological disease is based on at least 5 major premises:

(*i*) *Indirect evidence*. The presence of bacteria, viruses, parasites, fungi, nematodes or other organisms has never been proved in anterior uveitis except in rare cases. However, this negative evidence still awaits examination by electron-microscopic studies.

(*ii*) *Direct evidence*. Implicating immunological and allergic reactions in patients with uveitis, e.g. Hallett *et al.*[2] have shown that patients with uveitis have a high incidence of complement to uvea, compared with patients with other ocular disease and persons with normal eyes.

(*iii*) The close association of uveitis with diseases thought to be due to immunopathology, e.g. rheumatoid arthritis, ankylosing spondylitis and various collagen diseases.

(*iv*) Atopic uveitis, e.g. after ingestion of beef protein and in patients hypersensitive to animal dander, house dust and pollen. These are rare instances.

(*v*) Experimental evidence that ocular tissues, and in particular the uvea, are able to support the typical Arthus phenomenon, delayed hypersensitivity, transplantation-immunity (with corneal grafting) and auto-allergic mechanisms, e.g. to lens and uveal proteins. Uveitis can be produced experimentally by immunological techniques.

Before proceeding further it is necessary to state certain general considerations concerning allergy as it affects the eye. For an organ to react immunologically it is necessary for it to be exposed to an antigenic substance, to develop a hypersensitivity state to that substance and then, at a subsequent exposure to the same antigen, an immunological reaction occurs. The hypersensitive state may be mediated by antibodies present in the circulation (humoral antibodies) or by sensitized cells that are present locally in the organ (delayed hypersensitivity).

The eye is unique in being precluded from immunological injury by humoral antibodies because of the so-called blood-aqueous and blood-vitreous barriers, which insulate the anterior humours from the immunological activity of the body as a whole. Therefore, immunopathological reactions in the eye must depend on the ability of the organ to produce immunologically competent cells and local antibody. Witmer,[15] using fluorescein-labelled antibody, has demonstrated experimentally the ability of the eye to react in this way and Wolcowicz *et al.*[3] were able to show that continuous production of antibody by ocular tissues after antigenic stimulation will occur in tissue culture of these ocular tissues. Also of interest is the well-known observation that the typical histological picture of a subsiding non-granulomatous uveitis is often dominated by a plasmacytosis, which suggests that local antibody formation is in progress.

After exposure of the eye to an antigen, for example by intra-vitreous injection of the antigen, the eye becomes red and congested and uveitis develops, presumably owing to a state of local hypersensitivity in which immunologically competent cells are produced and proliferate in the eye, especially the uvea, producing antibody. The eye then settles down, returning to a normal appearance, but the ability to react to the specific antigen by producing immunologically competent cells remains. If that eye is subsequently exposed to the same antigen, it will react by producing local antibody; this production of local antibody which remains 'fixed' in the eye and is thought to be an important factor in 'local ocular hypersensitivity' sensitized the eye to the systemically introduced antigen. One should point out that this same sequence of events, should it occur in a lymph node, would probably pass unnoticed and be regarded as subclinical, but because of the exquisite sensitivity of the visual function of the eye this degree of reaction will produce a recognizable clinical disease, manifesting very often as uveitis. It is by no means clear why the uvea is so often the shock organ in the eye.

Silverstein[4] puts it as follows: 'Hence the act of antibody production in the eye may represent a contributing factor in the pathogenesis of uveitis'.

It is postulated that repeated exposure of an eye already sensitized to a specific antigen will produce repeated episodes of local immunological reactions affecting predominantly the uvea and these will be interpreted clinically as repeated attacks of non-granulomatous uveitis. It is possible that a similar mechanism may be implicated in repeated attacks of granulomatous uveitis.

EXPERIMENTAL EVIDENCE FOR UVEITIS OWING TO LOCAL ORGAN HYPERSENSITIVITY

Parenteral administration of an antigen does not in general result in a lesion from this first exposure. The antigen is fairly rapidly removed from the site of the injection and disseminated throughout the body so that by the time the immunological response has developed there will be no antigen remaining at the original site, but this is not so in the eye.

A week or 10 days following the injection of a soluble protein antigen into the vitreous body, a spontaneous uveitis develops in the injected eye which is characterized by lymphocytes and monocytes in the early stages and plasma cells later.[5] The vitreous body forms a natural depot for antigenic products,[6] and their slow escape (through the injection site) allows hypersensitivity to develop while the antigen is still present in the eye.

Following an attack of uveitis the eye returns to normal, but recurrent attacks can be produced for many months afterwards by injecting either intravenously or intracuta-

neously or ingesting the *specific* antigen, as the response is highly specific for the antigen.

The eye is normally insulated from circulating proteins. One may, therefore, ask how an antigen may enter the eye and sensitize ocular tissue, which constitutes the first stage of local ocular hypersensitivity. According to Silverstein[4] there are 2 possibilities:

(*i*) The most obvious is that the antigens involved in the pathogenesis of uveitis are proteins within the eye, e.g. lens and uvea, and that uveitis is an auto-allergic disease.

(*ii*) During the course of a mild bacteraemia accompanying an infection elsewhere, a few organisms may lodge in the uvea and reside there for a time, resulting in local sensitization. Penetration of organisms or protein into the eye would be facilitated by trauma or during ocular inflammation.[7] Woods[16] believes that most cases of non-granulomatous uveitis are due to local hypersensitivity to streptococcal protein.

To these 2 possibilities I shall add a third and fourth:

(*iii*) That the blood-aqueous and blood-vitreous barrier can be breached by a high concentration of circulating antigen so that antigen or a non-protein substance (hapten) may gain access to the ocular humours and, if a hapten, combine with a protein, e.g. lens or uvea, to form an antigen.

(*iv*) The antigenic potential of even minute quantities of antigen that gains access to the eye may be enhanced considerably by an immunological adjuvant such as bacterial protein, which may be present during a bacteraemia from an area of infection outside the eye.

These 2 postulates are strongly supported by experimental work.

Uveitis can be produced in guinea-pigs following parenteral sensitization and challenge of the animals with heterologous uveal protein injection into multiple sites. The uveitis occurs more frequently and the reaction is enhanced if complete Freund's adjuvant is mixed with the antigen. In this experiment uveal protein is delivered in high concentration so that it can gain access to the eye through the blood-aqueous and blood-vitreous barriers while its antigenic potential is enhanced by the use of complete Freund's adjuvant.[8]

A similar but more intense reaction is obtained when the challenging dose of uveal protein is delivered subconjunctivally to a previously sensitized animal; the reaction is considerably greater when Freund's adjuvant is given at the same time but at a different site (thigh). Ocular trauma alone, i.e., without delivering uveal protein, produces no reaction in the eye.[8] Of great interest is the fact that under these experimental conditions the degree of uveitis bears no relationship to the presence of circulating antibody and if this is present, to its concentration.[8] It seems, therefore, that under the conditions of this experiment the presence of circulating antibody constitutes no protection against local ocular hypersensitivity.

The application of this experimental fact to uveitis in man is important. One would like to know whether the degree of uveitis in man bears any relationship to the presence (and, if present, the concentration) of circulating antibody. If the postulate of local ocular hypersensitivity is correct, then circulating antibody should protect the eye from an attack of uveitis by removing systemic antigen. Hence severe uveitis should be associated with a low or absent serum antibody titre.

We are indebted to Woods[16] for the suggestion that non-granulomatous anterior uveitis is an allergic disease. He postulated that in most cases it is a reaction to streptococcal protein of the delayed bacterial type, based on his observation that in patients with non-granulomatous uveitis, 89% had positive skin tests to various strains of streptococcus, while in a control group with granulomatous uveitis only 20% were hypersensitive. The iritis improved when desensitization was attempted. Woods[16] believed the uvea became sensitized by streptococcal protein in the blood derived from an area of focal sepsis and when re-exposed to the antigen during a subsequent bacteraemia, acute uveitis developed. This postulate is not generally accepted because:

(*i*) Results of skin tests must be viewed with caution. A positive result does not necessarily indicate specific hypersensitivity of a particular tissue because non-specific skin reactions, owing to impurities in the preparation of the antigen, are not uncommon. Fair skins react more intensely than dark skins, and the reaction depends also on the amount of local histamine in the skin or circulating inhibiting drugs, e.g. corticosteroids.[9] Finally Lawrence[10] showed that positive skin reactions to streptococcal proteins occur in a relatively large segment of a random hospital population.

(*ii*) Studies on antistreptolysin titres on serum and aqueous humour of patients with uveitis have been inconclusive.

(*iii*) Attempts to produce microbial ocular allergy in animals have been unsuccessful.

If one accepts that uveitis is not due to microbial allergy, what allergens apart from endogenous ocular proteins might be responsible?

Uveitis is closely associated with certain generalized diseases such as ankylosing spondylitis, rheumatoid arthritis, Reiter's syndrome. A protein antigen, as yet undiscovered, may be the common aetiological factor. In this context the discovery of high titres of antibody to protein constituents of cow's milk in cases of ulcerative colitis with ankylosing spondylitis is of great interest.[11]

Finally there is the suggestion that the antigen responsible for uveitis is an endogenous ocular protein, e.g. lens protein, uveal or perhaps retinal, and that uveitis is therefore an auto-allergic disease. Two possible types of auto-antigen must be considered.

(*i*) Autologous proteins truly antigenic to the host.

(*ii*) Altered autologous proteins, which in their own natural state are non-antigenic.

Silverstein[4] suggested that lens protein is truly antigenic to the host and that exposure of the host to his own unaltered lens protein will cause a local phaco-anaphylactic reaction, as described by Verhoeff and Lemoine.[12]

Sympathetic ophthalmia on the other hand is due to sensitization of the individual to altered autologous uveal protein.[4]

The assumption that autologous lens protein is antigenic to the host whereas uveal protein in unaltered form is not, is based on the belief that lens protein is isolated from the

rest of the eye and the body early in development, so that it behaves as a 'foreign' protein, whereas normal uveal protein is not so insulated and therefore not 'foreign'. It has been shown, however, that lens protein is not confined to the lens, but is more widely distributed in the eye[13] and that antibodies to lens can be demonstrated in the serum of normal persons.[14]

My own experiments suggest that lens protein, at any rate in the guinea-pig, is a very weak antigen and to produce phaco-anaphylaxis it has to be boosted with adjuvant. Burky[15] came to the same conclusion in 1934. This can be demonstrated experimentally as follows:

The lens in one eye of a guinea-pig is needled, thus exposing the eye to autologous lens protein. Ten days later the second eye is needled and both eyes are examined histologically a week later. If Freund's adjuvant is not used, a mononuclear reaction develops in the second eye; however, if complete Freund's adjuvant is injected into the thigh at the same time the second eye is needled, the histological picture is characterized by a polymorphonuclear reaction as in the human disease.

Sympathetic ophthalmia can be produced experimentally by injecting heterologous uveal protein into the vitreous or subconjunctivally into previously sensitized guinea-pigs. Where lens protein is used instead of uveal protein, experimental sympathetic ophthalmia does not develop.

Apart from this experimental evidence that phaco-anaphylaxis and sympathetic ophthalmia may have an auto-allergic aetiology there is also clinical evidence:

(*i*) Temporal aspects, for example an initial exposure of the eye to lens protein may be followed after a latent period by phaco-anaphylaxis if the eye is re-exposed to lens.

(*ii*) Patients with phaco-anaphylaxis exhibit antibodies to lens protein in their serum.[19]

(*iii*) Woods[16] demonstrated anti-uveal antibodies in patients with perforating injuries of the globe.

(*iv*) Extracts of uveal tissue elicited a positive intradermal hypersensitivity test in patients with sympathetic ophthalmia. Woods[16] and Friedenwald[17] showed that the histology of the intradermal test was similar to that of the choroidal lesions. Witmer[18] demonstrated local antibody to uvea in a case of sympathetic ophthalmia.

(*v*) Hypersensitivity to lens protein antigen has been transferred from a patient with phaco-anaphylaxis to guinea-pigs.[19]

SUMMARY

Hypersensitivity to protein and in particular uveal and lens protein can fairly be stated to play a major role in the aetiology of uveitis. The evidence for this is:

(*i*) *Direct*: in the form of clinical characteristics of the disease, especially phaco-anaphylaxis and sympathetic ophthalmia and the evidence for an immunopathological reaction.

(*ii*) *Experimental*: of which there is a substantial and impressive body of evidence and

(*iii*) *Indirect*: as no other aetiological agent has been discovered in spite of intensive investigations.

The offending antigen or antigens may be a bacterial protein producing a delayed hypersensitivity reaction in the eye, although this is unlikely for reasons presented in this paper or the more likely possibility of an endogenous ocular protein, either boosted by an adjuvant or modified. This type of auto-allergic disease is manifested most strikingly in phaco-anaphylaxis and sympathetic ophthalmia, but may be responsible for other types of uveitis as well. Finally an exogenous protein may be responsible that is able to produce multiple organ immunopathology as for example, in rheumatoid arthritis, ankylosing spondylitis or Reiter's syndrome, the ocular lesion being part of a generalized disease process. It is possible that one or more, or all of these antigens, are responsible for the disease, but in the present state of our knowledge one can say no more than this.

Whatever the antigen responsible, local ocular hypersensitivity probably plays the major role in the pathogenesis of the disease and explains the recurrences alternating with complete remissions so characteristic of the disease. This type of immunological response, almost unique to the eye, is the result of certain anatomical and physiological factors which are peculiar to the eye. However, one must bear in mind that in experimental uveitis in guinea-pigs, the degree of uveitis bears no relationship to the level of circulating precipitins.

No doubt, as research into uveitis continues, the importance of these unique anatomical and physiological properties and the unusual immunological characteristics of the eye will emerge as important aetiological factors in non-granulomatous uveitis, although they do not explain why the uvea is so often the shock organ. In the granulomatous form of uveitis, in which active infection with an organism occurs, hypersensitivity probably plays an important accessory role in the formation of the granulomatous lesion although the evidence here is not as convincing as that which exists for non-granulomatous uveitis.

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