# AUTO-IMMUNE RESPONSE TO LENS AND UVEAL PROTEIN

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The allergic state was first described by Von Pirquet[1] in 1903 as the 'changed capacity of an individual to react to a foreign substance'. It has subsequently been pointed out that the 'substance' need not be foreign, that is, the individual may react to one of his own proteins and this reaction is called 'auto-immune disease'.

The allergic reaction is based on a combination of antigen with antibody which results in the individual developing a hypersensitivity to the antigen. A number of different reactions may occur depending on the type of antibody present. Smooth muscle and blood vessels are predominantly affected, resulting in spasm or necrosis.

The present belief is that the presence of foreign material, or in the case of auto-immune disease, autologous material, in the blood-stream is followed by an immediate cellular response by the reticulo-endothelial system, particularly lymphocytes and plasma cells. Diffusible material is absorbed into the cell and eliminated, but if not diffusible, it acts as an antigen stimulating the production of antibodies, which are globulins. These are carried in the cell, and if present in sufficiently large amounts, diffuse into the circulation after some days as 'circulating antibodies'. These circulating antibodies may be responsible for the local hypersensitivity reaction, e.g. delayed intradermal skin tests.

It has long been thought that an immune response can be elicited to autologous lens and uveal protein. As yet these are the only ocular proteins which appear to possess auto-immune properties.

## REVIEW OF THE LITERATURE

The concept of auto-immune disease had only just emerged when Von Szily[2] (1913) claimed that needling both lenses of a guinea-pig with an interval of 2 weeks between each needling resulted in the animal dying in anaphylactic shock. This was one of the first demonstrations of auto-immune disease in an experimental animal and also showed that the disease could be lethal. However, this claim has never been confirmed although many investigators, including myself, have attempted to repeat it.

Shortly after this report the American ophthalmologists Verhoeff and Lemoine[3] (1922) described and recognized the first cases of endophthalmitis phacoanaphylactica. These were cases of uveitis which appeared to result from an immune reaction to autologous lens protein. There rapidly emerged two schools of thought; those who followed Verhoeff and Lemoine and considered the iritis to be an anaphylactoid reaction to lens protein, and those who considered the evidence inadequate and suggested a toxic reaction to lens protein. Characteristically the eye first exposed to lens protein remains quiet. The histological picture in the other eye subsequently exposed to lens protein is unique, and patients exhibit a delayed intradermal reaction to lens protein in all cases.

Goodman,[4] in a series of 700 cases, showed that an equally severe skin reaction occurred in 5% of persons with uncomplicated senile cataract. Woods,[5] testing 75 normal persons, stated that the skin test was negative in all. My own experience has been similar to that of Woods. No skin biopsies were done. Histologically affected eyes are characteristic, showing a predominantly neutrophilic, mononuclear and epithelioid cell invasion centred around the fragments of lens tissue. Eosinophils are usually plentiful, and at the periphery of the lesion is a zone of lymphocytes and plasma cells.

Breinen[6] observed that in certain persons treated by injection of fish lens protein, subsequent removal of the lens (of the first eye) was followed by a typical endophthalmitis phacoanaphylactica, suggesting that they had been sensitized by the fish lens protein, which has some common antigens with human lens.[7]

Experimentally there is evidence that lens contains proteins capable of eliciting an antibody response in experimental animals of heterologous[8] and homologous[9] species. But rabbits with high antibody titres to homologous lens protein in their serum and aqueous humour did not develop lesions of the lens. When these rabbits were bred and high lens antibody titres maintained throughout pregnancy no significant congenital lesions were found in the offspring.[9]

Burky,[10] attempting to reproduce lens-induced uveitis, sensitized rabbits to lens protein by injecting homologous lens protein combined with staphylococcal toxins as an adjuvant. When these sensitized animals were subjected to discission of their lenses the operated eyes developed an acute inflammatory reaction, but histologically this did not resemble endophthalmitis phacoanaphylactica. The reaction was monocytic rather than neutrophilic, while the lymphocyte and plasma cell response was poor.

Another ocular protein which has been investigated for its antigenic properties is uvea. This interest dates from the suggestion of Elschnig[11] in 1911 that sympathetic ophthalmia is related to the development of a hypersensitivity to a specific substance, and the experiments of Woods[12] suggested that homologous uveal pigment was the offending antigen. He claimed that patients who developed sympathetic ophthalmia became hypersensitive to pigment at one stage of their disease. Friedenwald[13] studied biopsies of this delayed skin reaction and concluded that the histological picture resembled that of the choroid in sympathetic ophthalmia.

Attempts to stimulate antibodies to heterologous uveal tissue and pigment have been successful, but not to the homologous protein. Sympathetic ophthalmia has not been successfully produced experimentally nor has a hypersensitive state been transmitted from patients with the disease.

Recently Menk[14] produced an inflammatory reaction in rats' eyes by injecting systematically an anti-rat-eye serum prepared in rabbits. After 5 days he joined these rats parabiotically with healthy eyed normal rats. About 8 days later the eyes of the normal rats began to develop inflammatory ocular changes similar to those shown by the rats with primary ocular disease. There were no changes in the other body tissues. Control studies were negative. Menk concluded that the ocular inflammation was caused by auto-antibodies to eye tissue which had a definite specificity. These experiments support an important premise in the theory of auto-immune disease in the eye, namely that auto-antibodies to some ocular tissue are formed as the result of a sterile inflammation, and that these antibodies can react with native, unchanged tissue.

The hypothesis that sympathetic ophthalmia is due to a hypersensitivity to uveal pigment is attractive, particularly as attempts to isolate a causal organism have been unsuccessful. Unfortunately the present evidence, although suggestive, is not conclusive.

De Veer[15] reported 3 patients with sympathetic ophthalmia, in all of whom the supposedly exciting eye had been enucleated. When sectioned the anterior segments showed the classical histological picture of endophthalmitis phacoanaphylactica, and the posterior segments were characteristic of sympathetic ophthalmia. It seemed that the endophthalmitis phacoanaphylactica had antedated the sympathetic ophthalmia. He also pointed out in 1953 that the clinical picture of lens-induced uveitis in the second eye and sympathetic ophthalmia were similar and that many eyes with lens-induced uveitis

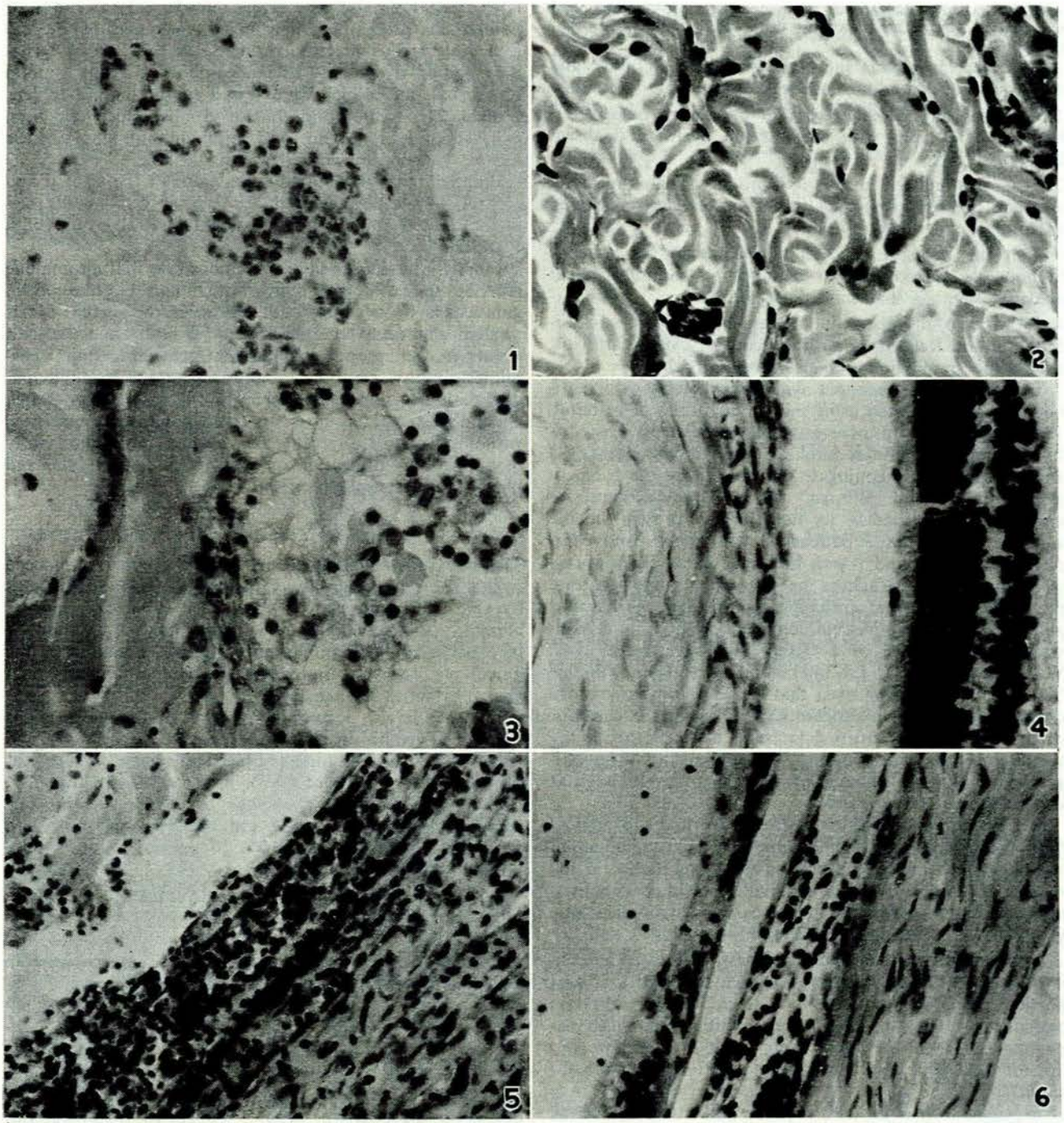


*Fig. 1.* Histology after 24 hours of skin nodule from guinea-pig belonging to 'treated group'. Mainly neutrophilic infiltration with gross tissue and cellular necrosis. (H. & E. × 128.)

*Fig. 2.* Histology after 24 hours of skin nodule from guinea-pig belonging to 'control' group. Mainly hystiocytic response with little tissue and cellular necrosis. (H. & E. × 128.)

*Fig. 3.* Photomicrograph showing lens and lens capsule of a guinea-pig sensitized to autologous lens protein without Freund's adjuvant. Predominantly mononuclear reaction with negligible neutrophil, lymphocyte and plasma cell infiltration. (H. & E. × 250.)

*Fig. 4.* Histology of choroid of guinea-pig sensitized to autologous lens protein without Freund's adjuvant. The appearance is normal. (H. & E. × 250.)

*Fig. 5.* Photomicrograph of anterior chamber of guinea-pig sensitized to autologous lens protein with Freunds' adjuvant. There is a predominantly neutrophil reaction with many eosinophils, lymphocytes and plasma cells in the anterior chamber, iris and lens similar to the appearances of endophthalmitis phacoanaphylactica in man. (H. & E. × 250.)

*Fig. 6.* Histology of the choroid in a guinea-pig sensitized to autologous lens protein with Freund's adjuvant. The choroid is oedematous and infiltrated with neutrophils, eosinophils, lymphocytes and plasma cells, similar to the appearance of the choroid in endophthalmitis phacoanaphylactica in man. (H. & E. × 128.)

Figs. 1 and 2 are reproduced from Luntz and Wright (1962): Exp. Eye Res., **1**, 317, with the kind permission of Academic Press Inc.

were mistakenly diagnosed as sympathetic ophthalmia and enucleated. This is an important differential diagnosis to bear in mind.

It is clear from this short review of the literature that some vital questions are still unanswered.

1. Are lens antibodies present in the serum or aqueous humour of persons with lens-induced uveitis and absent in normals?

2. Can lens-induced uveitis be produced experimentally and can the sensitive state to lens protein be transferred to another experimental animal?

3. Can the presence of lens antibodies in the aqueous humour be responsible for cataract formation? Present evidence suggests that this is not so.

4. Is an auto-immune reaction responsible for the manifestations of Reiter's syndrome, namely, uveitis, arthritis, ankylosing spondylitis and ulcerative colitis?

Techniques have become available whereby weak antibodies can be detected using minute quantities of material. The most useful of these are the Ouchterlony agar diffusion technique, the red cell haemagglutination method and the fluorescein conjugate method. Using the haemagglutination method, Witmer[16] was able to demonstrate agglutinating antibodies to human lens protein in the aqueous humour of 3 patients, 2 with uveitis and complicated cataract, and 1 with traumatic cataract. In a case of sympathetic ophthalmia he was able to demonstrate the presence of uveal antibodies in the aqueous humour and by using the fluorescein conjugate method, he demonstrated the presence of a 'fixed' antibody in the uvea. Witmer believes it is the interaction of antigen with this 'fixed' antibody in the uvea that causes the inflammatory change. He did not investigate normal persons as controls, so that he was not justified in being dogmatic about the significance of these findings. At present he is investigating the aqueous humour of all cases of uveitis seen at Zurich—some 400 a year.

Dr. Wright and I,[17] working at Oxford, have applied both the Ouchterlony method and the haemagglutination technique to search for lens and uveal antibodies in the sera of normal individuals and patients with endophthalmitis phacoanaphylactica, phacotoxic uveitis, phacolytic glaucoma, senile cataract and anterior uveitis.

Antibodies to human and calf lens protein were present in 57% of patients with lens-induced uveitis and in a proportion (30%) of patients with senile cataract. In one patient in whom a diagnosis of endophthalmitis phacoanaphylactica was made they were present in a serum dilution of 1/20,000. The lenses were removed by the intracapsular method so that I was unable to observe effects of exposure to lens proteins in these patients. Only two of 75 normal persons had lens antibodies.

Uveal antibodies were present in 70% of cases of lens-induced uveitis. There were none in normal persons or in patients with senile cataract. We also demonstrated that the hypersensitive state in the patient with endophthalmitis phacoanaphylactica could be transferred to guinea-pigs by injecting whole leukocytes from this patient subcutaneously into 6 guinea-pigs (treated group). A second group of six guinea-pigs received whole leukocytes from a normal individual (control group). Twenty-four hours later these animals were given intradermal injections of human lens protein and needling of their own lenses, and a typical Arthus reaction occurred in the treated series. Sera pooled from these 12 guinea-pigs and from a group of normal guinea-pigs were tested for antibodies to lens protein. The treated and control groups, which had been exposed to lens protein, had antibodies to lens in their serum, whereas the normal group did not.

Biopsies from these Arthus reactions in the treated and control guinea-pigs showed the typical cellular necrosis in the treated animals but not in the control group (Figs. 1 and 2).

Finally I have been able to demonstrate that an immune reaction to autologous lens protein can be induced in guinea-pigs by needling both lenses. If the second eye is needled at weekly intervals after the first, an acute iritis occurs in the second eye, the first remaining quiet. Histologically this reaction in guinea-pigs is similar to endophthalmitis phacoanaphylactica in man only when Freund's adjuvant is used. In those guinea-pigs sensitized without Freund's adjuvant the reaction is predominantly mononuclear—infiltration of neutrophils, lymphocytes and plasma cells is negligible (Figs. 3 - 6).

SUMMARY

There is substantial evidence that cases of lens-induced uveitis show hypersensitivity to lens protein and that this hypersensitive state can be transferred to an experimental animal; also that lens protein in the presence of adjuvant is capable of inciting an auto-immune reaction in the guinea-pig, similar histologically to endophthalmitis phacoanaphylactica in man.

Evidence is also accumulating of auto-immune reactions in cases of uveitis apart from sympathetic ophthalmia and lens-induced uveitis; for example, Hallet *et al.*[18] investigating a random sample of uveitis patients, showed that 52% of their sera were positive when tested for auto-immune complement fixation, while only 32% of persons with other ocular diseases and 10% of normal controls were positive.

These results are sufficiently encouraging to justify a large-scale investigation of auto-immune disease to lens and uveal protein as an aetiological factor in uveitis; not only in cases of uveitis as an isolated disease but also in association with generalized disease, e.g. Reiter's syndrome, ankylosing spondylitis, ulcerative colitis. This investigation would undoubtedly add much to our knowledge of these obscure diseases.

At this stage one might ask whether anything I have said is of clinical value. Our knowledge of auto-immune disease in the eye is at present too scanty to answer this fully; but even at this stage there are obvious important clinical applications. For instance, it has been shown that some cases of uveitis are almost certainly a result of auto-immune disease. This is a striking contribution to its aetiology which at present is obscure. Many more cases of uveitis must be investigated along the lines I have described, but it is reasonable to suppose that allergy will emerge as an important factor in the aetiology of both anterior and posterior uveitis. Once this has been established and offending antigens recognized, treatment can

be undertaken on a specific basis to supersede present-day random therapy.

The tanned red cell and Ouchterlony precipitation tests are useful in the differential diagnosis of lens-induced uveitis and sympathetic ophthalmia. This presents a difficult differential diagnosis and is of great importance, since the treatment for lens-induced uveitis is lens extraction and steroids, and the treatment for sympathetic ophthalmia is enucleation. With reports of sympathetic ophthalmia following iridencleisis operations on the increase, it would seem reasonable to investigate patients awaiting operation for uveal antibodies in their serum and/or aqueous humour and to avoid this operation in patients with antibodies. It appears reasonable to investigate patients in whom an extracapsular lens extraction is planned, and to plan an intracapsular extraction in those patients who exhibit antibody.

An approach along these lines would considerably reduce the incidence and aftermath of crippling uveitis following surgery or trauma.

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