

# Autoimmunity and the retina

## II. Raised serum IgM levels in retinitis pigmentosa

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Retinitis pigmentosa is a slow degenerative disease of the retina, almost invariably bilateral, beginning in childhood and often resulting in blindness in middle or advanced age. The clinical features of this disease and its mode of inheritance are well known, but the paucity of information concerning associated biochemical changes is such that we have virtually no knowledge of its aetiology (Campbell and Tonks, 1962). The degeneration of the neuro-epithelium of the retina which is the hallmark of the disease is regarded as being a form of abiotrophy in man (Treacher Collins, 1919). Since the disease occurs in two forms—one hereditary and the other not—and there are many atypical forms on record, it is possible that this disease is in fact a syndrome and that the damage to visual cells is a symptom complex brought about by a variety of causes, all leading to similar types of organic changes, because the retina, being a specialized tissue, can react pathologically in only a limited way.

Since our demonstration of the antigenicity of the photoreceptors in the retina (Rahi, 1970), two different laboratories have reported on the pathogenetic role of retinal antigens in ocular inflammation and have supported our views on the subject (Wacker and Lipton, 1971; Tilgner, Meyer, Hempel, and Schröder, 1973). Since it seems certain that retinal tissue is antigenic, it would not be illogical to assume that, in at least some cases of retinal degeneration, an immunological injury may be responsible either partly or wholly for such a change. Campbell and Tonks (1962) studied the biochemical profile of retinitis pigmentosa patients in England and concluded that there was no gross abnormality in serum proteins. The level of gamma globulin, however, was over 1 g. per cent. in about half the cases analysed. Bondareva (1969), writing from Russia, noted a disturbance in the serum proteins of such patients and showed a decrease in the albumin/globulin ratio. Most exciting is the report from the U.S.A. on serum proteins in retinitis pigmentosa (Fessel, 1962). Of thirteen patients having the ophthalmoscopic appearance of this disease, five (38 per cent.) had a positive F II latex agglutination test. The protein responsible for this reaction is commonly found in rheumatoid arthritis and is known as rheumatoid factor. An ultracentrifugal study also revealed an elevation of the 19S macroglobulins in six of the ten sera examined. Since it is now known that IgM has a sedimentation coefficient of 19S and that the rheumatoid factor is chiefly an IgM, although this activity may be found in other immunoglobulin classes, such as IgG and IgA (Abraham, Clark, and Vaughan, 1972), it seemed imperative to study the various immunoglobulins, especially IgM, in patients with retinitis pigmentosa, in an attempt to uncover the nature of the suspected immunological abnormality which could perhaps explain the slow but sure degeneration of the visual cells in this condition.

## Material and methods

Patients with retinitis pigmentosa attending the genetic clinic of Moorfields Eye Hospital over the last 3 years, and some cases referred to us by local consultant ophthalmic surgeons, were included in the present series. Blood was collected from 52 such cases (29 males and 23 females) and the serum was tested fresh or stored at  $-30^{\circ}\text{C}$ . until used.

Immunoglobulins G, A, and M were quantitatively estimated using the radial immunodiffusion technique of Mancini, Carbonara, and Heremans (1965). W.H.O. reference serum code-labelled 67/99 (obtained from the National Institute for Medical Research, London) was used as standard. After the development of the precipitin rings, the immunodiffusion plates were washed and stained, using the technique described elsewhere (Chignell, Carruthers, and Rahi, 1971).

A standard curve was constructed by plotting the immunoglobulin concentration against the ring diameters on a semilog graph paper. The immunoglobulin concentrations of the test sera were read off this curve and the values were expressed in international units (i.u.)/ml.

Blood obtained from forty normal adults (20 males and 20 females) was also analysed in the same manner for the various immunoglobulins and the values obtained were used for statistical analysis of the test sera.

## Results

The levels of the various immunoglobulins in the sera of normal individuals and in those with retinitis pigmentosa are shown in Tables I and II.

**Table I** Serum immunoglobulins in control population

Immuno- globulins	Controls							
	20 adult males				20 adult females			
	Mean (i.u./ml.)	Range (i.u./ml.)	S.D.	S.E.M.	Mean (i.u./ml.)	Range (i.u./ml.)	S.D.	S.E.M.
G	115.39	58-184	29.73	6.65	116.59	58-184	30.8	6.89
A	147.04	72-238	47.64	10.65	151.14	71-267	59.00	13.19
M	121.79	58-207	37.98	8.49	148.49	57-207	37.46	8.37

**Table II** Serum immunoglobulins in retinitis pigmentosa

Immuno- globulins	Patients							
	29 males				23 females			
	Mean (i.u./ml.)	Range (i.u./ml.)	S.D.	S.E.M.	Mean (i.u./ml.)	Range (i.u./ml.)	S.D.	S.E.M.
G	124.89	61-216	38.63	7.17	139.39	71-203	40.14	8.36
A	143.86	65-285	57.15	10.61	140.86	42-253	57.86	12.06
M	202.34	88-345	76.62	14.22	236.34	116-345	65.80	13.72

There was no significant difference ( $T$  less than 1) in the serum levels of IgG and IgA between retinitis pigmentosa patients and the control group (Fig. 1).

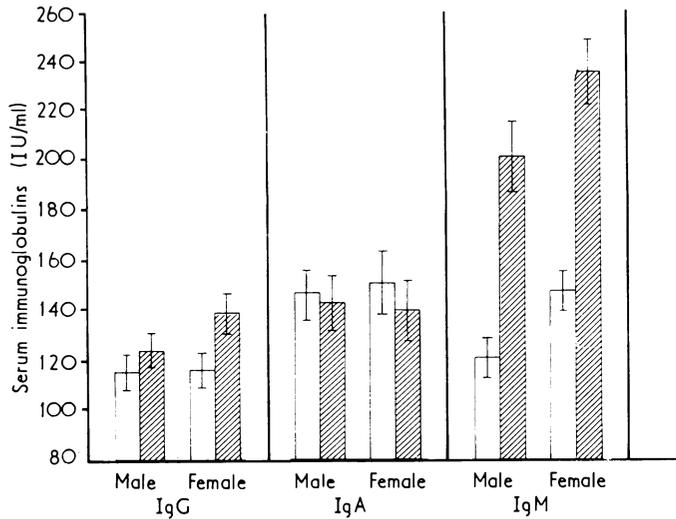


FIG. 1 Serum immunoglobulins in retinitis pigmentosa (stippled) and normal controls (clear)

IgM, however, was appreciably raised in a proportion of patients with retinitis pigmentosa. The mean serum IgM in male and female patients was 202 ( $\pm 77$ ) and 236 ( $\pm 66$ ) i.u./ml. respectively. The corresponding mean values in the control group were 120 ( $\pm 38$ ) and 148 ( $\pm 37$ ) i.u./ml. The difference is statistically significant (Table III).

**Table III** Analysis of the significance (IgM values: control v. sample)

Variables	Mean Values	$T$	$P$
Male Control	121.79	4.81	Less than 0.001
Male Sample	202.34		
Female Control	148.49	5.09	Less than 0.001
Female Sample	236.34		

The frequency distribution of the two groups shows considerable overlap, but there appears to be a special population of retinitis pigmentosa subjects which stands out distinctly with a raised IgM (Fig. 2, opposite).

### Discussion

The reason for the degeneration of the photoreceptor cells remains an enigma, but it is widely believed that it is due to an abiotrophic process (Treacher Collins, 1922). Whether the process of abiotrophy is affected by extraneous influences is not known, but the possibility should by no means be ruled out (Duke-Elder and Dobree, 1967). An ophthalmoscopic appearance closely resembling pigmentary dystrophy may be associated with virus infections such as rubella and measles. A similar secondary change sometimes appears as a complication of vaccination (Redslob, 1947) and Behçet's disease (Strucchi and Vollenweider, 1958), and is sometimes associated with Harada's disease. Visual cell degeneration has also been observed in some cases of polyarteritis nodosa (Dejean

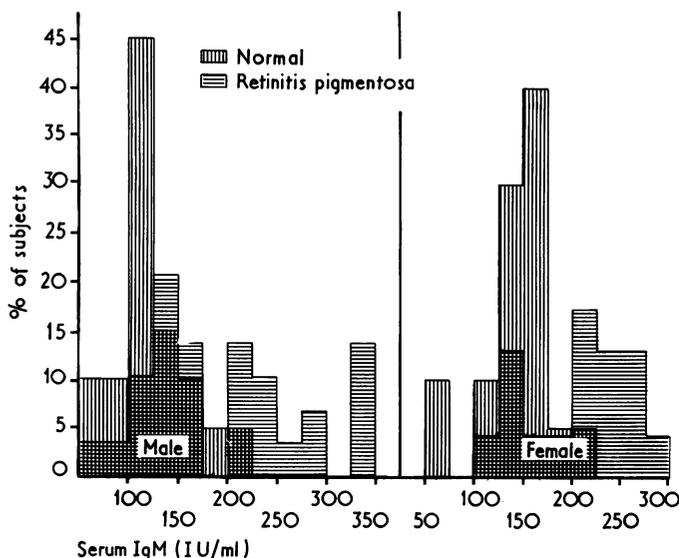


FIG. 2 Distribution of serum IgM in cases of retinitis pigmentosa

Viallefont, and Champion, 1953), multiple sclerosis (Riechert, 1933), and rheumatoid arthritis (Mathias, 1955). It is interesting to note that rheumatoid arthritis, Harada's disease, multiple sclerosis, and polyarteritis nodosa are considered to have an allergic aetiology, and that an abnormal immunological response is not uncommon after vaccination and Behçet's disease.

The raised levels of IgM in the present series would seem to suggest an infective or autoallergic process in retinitis pigmentosa, but high levels are found in a variety of other ocular disorders, notably uveitis (Aronson, 1968), endocrine exophthalmos (Mahaux, Delcourt, Chamla-Soumenkoff, and Nagel, 1969), Sjögren's syndrome (Talal and Bunim, 1964; Feltkamp and Van Rossum, 1968), and retinal vasculitis (Chilman, 1973). Since it is known that autologous IgM can lyse neuraminidase-treated host cells, it is argued that naturally occurring cytotoxic antibodies of this class could be important in the process of ageing (Rosenburg and Rogentine, 1972). The phenomenon of senescence and the damaging (*i.e.* age-accelerating) effect of immune reactions have been reviewed by Burnet (1970). Since selective degeneration of visual cells is not a feature of old age, it is difficult to regard retinitis pigmentosa as a product of premature senility, and the role of raised IgM therefore remains unexplained. IgM tends to appear very early in an immunological response and is often superseded by IgG. It is synthesized, however, for much longer periods of time, especially in response to particulate antigens. It has been found to be more potent than IgG in dealing with antigens associated with cell surfaces because of its superior complement-fixing property (Humphrey and White, 1970). IgM is raised during most infections, particularly of the virus and protozoal types, and a high level is not uncommon in sarcoidosis, cirrhosis, systemic lupus erythematosus, and chronic mucosal inflammations (Marks, 1972). Some of the isohaemagglutinins and many of the natural antibodies to micro-organisms and the Wassermann reaction antibodies in syphilis are found in this class (Roitt, 1971).

Since IgM is raised in a variety of conditions, both infective and non-infective, it is difficult to assign a definite role to it in the pathogenesis of retinitis pigmentosa. Moreover, the normal levels of IgM are found to spread over a wide range—a recent paper quotes a range of 47 to 380 i.u./ml. in the European community (Rowe, 1972)—and the levels are

usually higher in females than males (Wood, 1971).

Although histological evidence of vasculitis in retinitis pigmentosa is on record (Stock, 1937), most of the cases do not show any inflammatory reaction, the most marked changes being extensive gliosis, vascular sclerosis, and pigmentary disturbance. These features, therefore, seem to rule out completely an immunological injury to the retina in primary retinal dystrophies. A similar paucity of inflammatory reaction, however, is found in experimentally induced immune gastric atrophy (Hennes, Sevelius, Llewelyn, Joel, Woods, and Wolf, 1962), and a similar situation can be found in immune-complex nephritis in man (Bellanti, 1971); thus an immunological injury may not always be represented by inflammation.

Although a virus aetiology has not been suspected in cases of retinitis pigmentosa, it is difficult to rule out the possibility of a "slow virus" infection, the role of which is being assessed in such neurological diseases as multiple sclerosis and Parkinson's disease (Bellanti, 1971), and which is known to produce sub-acute and chronic degenerative disease of the central nervous system in man (Leading article, *B.M.J.*, 1973).

Since macular involvement has been observed in "slow virus" infections, Zimmerman (1970) has suggested that some purely retinal dystrophies, including some considered to be genetically determined, may be due to "slow viruses". Raised IgM in retinitis pigmentosa could therefore be suggestive of an occult (virus) infection.

One of the important functions of the visual cell is constantly to renew its outer limb, and it does so by forming new lamellated discs every day at the base of the outer segment (Young, 1971a); the old discs being pushed outwards are nipped off and removed by the pigment epithelium (Spitznas and Hogan, 1970; Young, 1971b). A virus infection, which is not cytolytic but is capable of modifying the function of the pigment epithelium and visual cells, could affect this process of renewal, so vital to the functional integrity of the retina. Such a state is not difficult to visualize since it is known that certain viruses can produce an "integrated" type of reaction in which virus DNA appears to become integrated with host-cell DNA in a fashion analogous to lysogenic bacteriophage interaction with bacterial cells. The host cell then appears to become transformed owing to some alteration in the cell regulatory mechanism (Bellanti, 1971). In the present state of our knowledge, it is difficult to substantiate a virus aetiology in retinitis pigmentosa, and it seems unlikely that a virus will affect the visual cells and/or the pigment epithelium directly and selectively.

Since the production of IgM is genetically controlled, and since large numbers of cases of retinitis pigmentosa are hereditary in origin, it is possible that individuals with raised IgM are more susceptible to retinal degeneration. This would mean that the immunological disturbance perhaps represents a further expression of the genetic abnormality that underlies retinitis pigmentosa.

### Summary

An attempt has been made, for the first time, to quantitate the serum levels of various immunoglobulins in a large series of cases of retinitis pigmentosa. Immunoglobulin M was significantly higher in 52 cases of retinitis pigmentosa than in a group of forty normal individuals. Whether the raised IgM is responsible for the retinal degeneration or is indicative of an occult (possibly virus) infection is not known. It is possible that individuals with raised IgM may be more prone to retinal degeneration. It is also conceivable that a raised IgM simply represents a further expression of the genetic abnormality which underlies most cases of retinitis pigmentosa.

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