COMMUNICATIONS

INVESTIGATIONS INTO HYALURONIC ACID AND HYALURONIDASE IN THE SUBRETINAL FLUID IN RETINAL DETACHMENT, PARTLY DUE TO RUPTURES AND PARTLY SECONDARY TO MALIGNANT, CHOROIDAL MELANOMA

Preliminary Report Suggesting a New Hypothesis Concerning the Pathogenesis of Retinal Detachment

BY

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INTRODUCTION

Although Meyer and Palmer isolated hyaluronic acid 15 years ago (1934), it was Chain and Duthie's discovery (1940) that the "spreading factor" is identical with hyaluronidase, the enzyme depolymerizing hyaluronic acid, which gave an impetus to the study of these biological substances. Hyaluronic acid constitutes

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an important element of a number of the refracting media of the eye, and it is only natural that various valuable ophthalmological papers dealing with this substance should already have been published. Thus investigations have been made into hyaluronic acid in the cornea, the aqueous humour, the crystalline lens (Meyer 1938, 1940, and 1948), and the vitreous body (Pirie et al. 1948, Pirie 1949). But no investigations into hyaluronic acid in the subretinal fluid are available.

The object of the present investigation has been to test the subretinal fluid for hyaluronic acid as well as hyaluronidase for the purpose, if possible, of throwing some light on the numerous problems regarding retinal detachment. Demonstration of the presence or absence of these substances in the subretinal fluid may perhaps contribute to the elucidation of the pathogenesis of retinal detachment (the question of the share which the vitreous body has in the subretinal fluid), its diagnosis (serous detachment versus secondary detachment in malignant melanoma from the choroid, or in exudative retinopathy); and furthermore, its prognosis (chance of healing after surgical diathermy). Last, but not least, it may open new vistas for supplementary medication with antihistamines.

Before proceeding to the present investigations I shall briefly recapitulate the results of investigations by other writers, as well as modern views concerning:

(1) the nature of the subretinal fluid; (2) the vitreous body; and (3) hyaluronic acid and hyaluronidase, with the main stress laid on conditions of importance for the following discussion. It is outside the scope of the present work to enter further on these subjects. Those interested may be referred to the comprehensive text-books (Duke-Elder) and the most recent articles in the journals (Meyer, Pirie).

THE SUBRETINAL FLUID IN RETINAL DETACHMENT

This fluid has been analyzed for a great number of physical as well as chemical properties, most recently and most thoroughly by Weve and Fischer (1937, 1939, and 1940), while hyaluronic acid and hyaluronidase investigations have not so far been reported.

The pathogenesis of the subretinal fluid is not quite clear. Most writers (Weve and Fischer) hold that the subretinal fluid consists mainly of vitreous body penetrating subretinally via the retinal rupture. This genesis is, however, denied by Magitot (1934). Koyanagi (1934) supposes the subretinal fluid to be secreted from the pigmentary epithelium of the retina. This
Hyaluronic Acid in Subretinal Fluid

Hyaluronic acid harmonizes with the theory that the main site of production of normal vitreous body is the pigmentary epithelium.

The passage of vitreous body via the retinal rupture is easily envisaged in cases displaying large ruptures at the ora, but these are rare. In detachment after small or even minimal ruptures it is more difficult to understand how vitreous body could penetrate, though indeed liquefaction of the latter may totally change the possibilities of transfer (see later).

If a retinal rupture is demonstrable—and careful examiners can nearly always find one—the subretinal fluid is relatively clear, yellowish, mucous and ropy, and it does not coagulate on standing. Where the detachment is of longer duration the albumin content will increase, possibly under the influence of transudation from the vessels of the choroid. In cases of very long-standing detachment the albumin may altogether disappear simultaneously with atrophy of the choroid (Duke-Elder). The part of the vitreous body which penetrates subretinally will undergo certain successive changes and become admixed with heavy water and protein from the choroid (Weve and Fischer 1940).

If the retinal rupture is not demonstrable (in these cases it is hardly a question of primary serous detachment, but rather of exudative retinopathy—whether locally induced or of systemic origin), then the subretinal fluid is highly coagulable, jelly-like, grey and albuminous, often with admixture of blood. This finding is analogous to inflammatory exudates in other parts of the organism.

In cases of malignant melanoma of the choroid the subretinal fluid is highly albuminous. The albumin yields the special yellowish colour visible on ophthalmoscopy (Ronne 1936). Adequate physico-chemical analyses of the subretinal fluid are missing in these cases.

In serous detachments analyses of the subretinal fluid have revealed great variations in the albumin concentration (about 135–60 per cent.), sugar values as in the vitreous body, and a chloride concentration differing from that of blood plasma (Duke-Elder). Jasiniki has made viscosity tests (1933). The following enzymes have been demonstrated: amylase (Weve and Fischer 1937) and acetyl-cholinesterase (Weve and Fischer 1939).

The Vitreous Body

The vitreous is not, as previously believed, of a cellular nature, but a gel comparable to a mass of plasma (Davson 1949). If the water is evaporated "residual protein" will remain, together with the polysaccharide hyaluronic acid—the latter being a
protein-free substance erroneously called mucoprotein in the past. These two non-haematogenous substances determine the special structure of the vitreous body (Pirie 1948 and 1949), in which the high viscosity is due to hyaluronic acid. The hyaluronic acid is responsible for 30 per cent. of the organic weight of the vitreous body (Meyer 1948).

Recent comprehensive analyses made on frozen sections of vitreous body showed in several respects a chemical resemblance to the aqueous humour (Duke-Elder and Davson 1949), but there was a great difference with regard to phosphate content (Palm 1948).

The vitreous body has been demonstrated to contain the following enzymes: amylase, proteinase, and acetyl-cholinesterase (Uvnäs and Wolff 1938). The action of these enzymes is accelerated by change of pH in the acid direction, and an autolysis may take place. Liquefaction of the vitreous body may also occur through haematogenous enzymes, notably hyaluronidase, which (see below) specifically depolymerizes the hyaluronic acid into low-molecular reducing agents.

**HYALURONIC ACID AND HYALURONIDASE**

Hyaluronic acid (Meyer and Palmer 1934) is present in the ground substance of connective tissue, the jelly of Wharton in the human umbilical cord, the synovia of joints, and abundantly in the vitreous. Smaller amounts exist in the cornea, aqueous and crystalline lens, but not in blood and cerebrospinal fluid. Chemically hyaluronic acid resembles the anticoagulant heparin. It is a high-molecular polysaccharide, a polymer of a disaccharide consisting of glucuronic acid and N-acetyl glucosamine (a hexosamine). The molecular weight has not been finally settled. It depends on the degree of polymerisation, but is within the range of 200,000 to 500,000. The hyaluronic acid, probably produced from the cells of the connective tissue (type not yet elucidated), presents as a mucous, highly viscid fluid. The high viscosity conditions the resistance of connective tissue (and other tissues) to passage of both corpuscular elements (bacteria, Indian ink particles) and liquefied substances (toxins, snake venom, etc.).

The enzymatic depolymerisation of the hyaluronic acid is due to the specific enzyme hyaluronidase (Chain and Duthie 1940), which is identical with the "spreading factor" previously demonstrated in extracts of testis, malignant tumours, snake venoms and bacterial cultures (Hofman and Duran-Reynals 1930, McClean 1930). Hyaluronidase is prepared from bull semen and is a high-molecular substance, which has not yet been produced in pure form. Addition of hyaluronidase to a viscid hyaluronic
acidsolution will cause a prompt depolymerisation of the hyaluronic acid into glucuronic acid and glucosamine, and the fluid will now become thin like water. The depolymerisation of the high-molecular hyaluronic acid into the low-molecular reducing disaccharides may in part be followed viscosimetrically, and partly by the power of reduction.

The sites of production of hyaluronidase are, in cases of infection, the bacterial elements, and, in cases of malignant tumours, presumably the supporting elements of the tumour tissue. Mayer and Kull (1947) have shown that an allergic tissue reaction, e.g., within a skin area, will involve local production of hyaluronidase, which, by its influence on the hyaluronic acid of the connective tissue, contributes to the allergic process—in this instance spreading of oedema. Mayer and Kull succeeded in inhibiting the hyaluronidase activity by antihistamines (pyribenzamine). This opens new prospects for our understanding of the allergic process and the possibility of supplementary therapy.

A quantitative estimation of hyaluronic acid is still difficult. Such is based partly on viscosimetry (Meyer; Dalgaard-Mikkelsen and Kvorning), and partly on reduction determination of the reducing depolymerisation products. The relation of viscosity to quantity is not yet elucidated. Hyaluronidase is estimated biologically by its effect on the hyaluronic acid, partly in vitro (viscosimetry) and partly in vivo by the rate of spreading of Indian ink particles injected subcutaneously.

**Present Investigations**

The series on which the present investigations are based comprises 17 patients with retinal detachment, whose data appear from Table 1. Some of the patients were admitted to the Kommunehospital and some to the Rigshospital, Copenhagen. There were 9 females and 8 males ranging in age from 16 to 65 years. The retinal detachment had the following causes: direct trauma in five cases (1, 2, 3, 4, 5), excessive myopia in five cases (6, 7, 8, 9, 10), uncertain or unknown cause in another five cases (11, 12, 13, 14, 15), of which, however, case 15 presented a generalized exudative disease: Besnier's prurigo with simultaneous syndermatototic cataract. In two cases (16, 17) the retinal detachment was secondary to a histologically verified malignant choroidal melanoma.

The extent of the retinal detachment is indicated in retinal squares, from one-fourth to four-fourths with the following distribution: two cases one-fourth (9, 13), seven cases two-fourths (1, 3, 5, 8, 11, 12, 16), three cases three-fourths (6, 7, 10), and finally five cases total detachment (2, 4, 14, 15, 17); thus a representative series.
TABLE 1—The relative viscosity of the subretinal fluid in 17 cases of retinal detachment

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age</th>
<th>Etiology</th>
<th>Size in squares</th>
<th>Tear</th>
<th>Duration in mths</th>
<th>The subretinal fluid</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F.</td>
<td>25</td>
<td>Traumatic</td>
<td>2/4</td>
<td>2</td>
<td>1</td>
<td>1:30</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M.</td>
<td>39</td>
<td>—</td>
<td>4/4</td>
<td>+</td>
<td>1</td>
<td>1:30</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M.</td>
<td>51</td>
<td>—</td>
<td>2/4</td>
<td>+</td>
<td>1</td>
<td>1:20</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F.</td>
<td>46</td>
<td>—</td>
<td>4/4</td>
<td>+</td>
<td>1/2</td>
<td>1:50</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M.</td>
<td>49</td>
<td>—</td>
<td>2/4</td>
<td>+</td>
<td>1/10</td>
<td>1:00</td>
<td></td>
</tr>
</tbody>
</table>
| 6        | M. | 46  | Excessive myopia | 3/4 | 2 | 1:30 | — | 1940 I detachment
          Now 1949 re-operation |
| 7        | F. | 43  | —        | 3/4             | +    | 1               | 1:40                 | 1) from the bulk + tear |
| 8        | F. | 54  | —        | 2/4             | +    | 1/10            | 1:20                 | 2) from the bulk — tear |
| 9        | F. | 44  | —        | 1/4             | +    | 1/2             | 1:10                 |          |
| 10       | M. | 29  | —        | 3/4             | +    | 1               | 1:10                 | Total detachment in the other eye previously |
| 11       | F. | 23  | Questionable | 2/4 | — | 1:30 | — |          |
| 12       | F. | 65  | —        | 2/4             | +    | 1               | 1:30                 |          |
| 13       | F. | 62  | —        | 1/4             | +    | 3               | 1:30                 |          |
| 14       | F. | 50  | —        | 4/4             | +    | 18              | 1:10                 | Case of re-operation Generalized exudative diathesis affecting the skin, etc., + cataract syndermatotica. Re-operation. |
| 15       | M. | 10  | Besnier's Prurigo | 4/4 | — | 1:0 | — |          |
| 16       | M. | 50  | Melanoma malignant choroid | 2/4 | — | 1 | 1:0 | — |          |
| 17       | M. | 35  | —        | 4/4             | —    | 8               | 1:0                  |          |

*Retinal rupture* was definitely found in thirteen cases, and suspected in two others. Rupture was not observed in four cases, of which two with melanoma and two of an exudative character (cases 1 and 15), the latter the one with Besnier's prurigo. The ruptures were in all cases rather small. Some were of the ordinary horse-shoe type, while others were of the cribriform, cystoid type. None of the cases presented disinsertion or large rupture at the ora serrata.

The *durations of the retinal detachments* were as follows: less than one month in three cases (5, 8, 9), one to three months in nine cases (2, 3, 4, 6, 7, 10, 12, 13, 16), and from three to eighteen months in three cases (1, 14, 17). In two cases the duration could
not be fixed (11, 15). The retinal detachment was treated by ordinary surgical diathermy (according to Larsson-Weve), except in the two cases with malignant melanoma, where enucleation was performed. Course and result will not be discussed here. During the operations the subretinal fluid flowing through the scleral perforations was collected and placed in a refrigerator. Possible admixture of larger or smaller amounts of blood proved to play no great part for the further investigation, since blood contains no hyaluronic acid.

The subretinal fluid was then tested as soon as possible for hyaluronic acid and hyaluronidase in the Department of Pharmacology, University of Copenhagen. These tests were performed by the viscosimetric technique recently elaborated by Dalgaard-Mikkelsen and Kvorning (1948). Although the method, the details of which appear in the original article, is a sensitive micro-method, a dilution of 1 in 10 of the subretinal fluid was chosen in the majority of the cases, in order to obtain a sufficiency of material for examination. The procedure consisted of placing the diluted, subretinal fluid in the specially constructed viscosimeter, where, at a constant temperature, the duration of flow through a capillary tube with a given lumen was measured in seconds. Three or four control measurements were made. The flow-time for distilled water is 80 seconds, but for diluted subretinal fluid flow-times up to 120 seconds have been noted. In the cases where the flow-times exceeded that for distilled water a little hyaluronidase was added to the solution, and then, after a few minutes' standing, another series of readings was taken. This brought about prompt reduction in the flow-time, e.g., from 120 to 90 seconds. The relative viscosity was calculated on this basis, and the values have been set out in Table 1.

The changes observed in the flow-times after addition of hyaluronidase can be due only to the fact that the previously viscid solution has changed its character in consequence of the depolymerisation of the hyaluronic acid. If the genuine, subretinal fluid presented flow-times approximately corresponding to that for distilled water, so that we may exclude the presence of hyaluronic acid, the solution was tested for hyaluronidase content by addition of a known standard solution with hyaluronic acid. In a small number of cases there was occasion to determine the relative viscosity of both undiluted and diluted (1:10) subretinal fluid. To give an idea of the reduction of the relative viscosity brought about by dilution it may be stated that relative viscosity 1:3 in dilution 1:10 corresponds to relative viscosity 4:0 in undiluted fluid. As, however, the present investigation aims only at a preliminary qualitative estimation, these facts will not be
discussed further. They will be dealt with in greater detail in future papers.

The relative viscosities in the subretinal fluid were as follows:

In the five cases of traumatic origin: 1.20-1.50 in four cases, and 1.0 in one case (5) (re-operated on).

In the five cases with excessive myopia: 1.10-1.40. In one case (7) the value was much higher in a sample from the site of rupture (1.40) than in one from another part, where no rupture was found (1.10).

In the five aetiologically uncertain cases: 1.30 in three, 1.10 in one (14) of re-operation, and 1.0 in one (15) presenting Besnier’s prurigo.

In the two cases of malignant choroidal melanoma: 1.0.

Since relative values of 1.10 or more are suggestive of the presence of hyaluronic acid, it appears that hyaluronic acid was found in all the cases of serous detachment, except two submitted to re-operation (5 and 14), and one of exudative retinopathy as part of a generalized exudative disease (Besnier’s prurigo). Hyaluronic acid was absent in both cases of malignant choroidal melanoma.

Hyaluronidase was demonstrable in none of the 17 cases.

Regarding the relation of the duration of the retinal detachment to the amount of hyaluronic acid, estimated approximately on the basis of the relative viscosity, it appeared that the highest relative viscosities—and thus the highest hyaluronic acid values—were found in the cases of 1 to 3 months’ duration. The cases of shorter and those of longer duration, on the other hand, presented lower relative viscosities, such comparatively small material must be cautiously interpreted.

There appears to be a definite correlation between retinal rupture and relative viscosity, since hyaluronic acid was present in all cases of rupture, except those re-operated on owing to recurrence, where special conditions asserted themselves.

**Discussion**

Although the present investigation is based on a rather small number of cases of retinal detachment, the results of the hyaluronic acid analyses in the subretinal fluid are fairly uniform. It appears that in primary, serous, retinal detachment the subretinal fluid contains considerable amounts of hyaluronic acid, which are responsible for the characteristic ropy and mucous character of the fluid. In cases of malignant choroidal melanoma with secondary retinal detachment, on the other hand, the subretinal fluid is not viscid, and hyaluronic acid could not be demonstrated. In two cases of recurrent detachment and one of
Hyaluronic Acid in Subretinal Fluid

exudative retinopathy as part of a generalized disease (Besnier's prurigo) no hyaluronic acid was found.

The fact that such large amounts of hyaluronic acid were demonstrated in all the cases of primary serous retinal detachment with ascertained retinal rupture bears out the hypothesis advanced by previous writers (Weve and Fischer) that the subretinal fluid comes from the vitreous body, the considerable hyaluronic acid content of which has been established (Pirie, Meyer). The fact that the hyaluronic acid concentration in the subretinal fluid seems small at first, and then gradually increases, may contribute to an understanding of the pathogenesis.

Our knowledge regarding retinal rupture and retinal detachment is still scanty, despite the enormous work done by various investigators in their attempts to find the factors giving rise to the lesions. The results of the present hyaluronic acid investigations as well as recent discoveries concerning the liberation of hyaluronidase by allergic vascular or tissue reactions (Mayer and Kull) are of such a nature that it may be tempting, on the basis of them, to set up a new hypothesis with regard to the pathogenesis of retinal detachment.

The cases where the pathogenesis is evident, i.e., the traumatic detachments (after perforating injuries, etc.) will here be left out of account. The trauma will often present the character of a triple-response reaction (Lewis Ebbecke), having many features in common with the allergic vascular reactions.

In other cases of retinal detachment, where direct physical trauma is absent, it may be of value to search for possible psychic trauma in the past history. The possibility of a psychosomatic origin of a disease is gaining ground within many branches of medicine, thereby explaining to an increasing extent why mental conflicts may often give rise to complicated somatic symptoms, presumably via certain diencephalically released angioneurotic lesions. The "general adaptation syndrome" recently described by Selye in both physical and mental "stress" likewise contributes to greater clarity. Many eye diseases (glaucoma, iridocyclitis, relapsing superficial keratitis, scleritis, detachments, etc.) of obscure origin may thus be elucidated and explained in a new manner.

Since hyaluronidase is liberated by allergic vascular reactions—as shown by Mayer and Kull—it is reasonable to suppose that an analogous angioneurotic vascular lesion, in a portion of peripheral retina, for instance, may cause similar liberation of hyaluronidase. The primary vascular lesion in the retina will involve a local ischaemia with consequent tissue necrosis, resulting in cystoid degeneration, which sooner or later will develop into a
rupture. The liberated hyaluronidase within the ischaemic area will depolymerize the hyaluronic acid in the adjacent vitreous body, the high viscosity of which will thereby become reduced. The attenuated vitreous body may now pass through the retinal rupture. The extent to which the vitreous body penetrates subretinally, thereby conditioning the development of retinal detachment, depends no doubt on various factors. A certain balance will occur between the two portions of the vitreous body on both sides of the retinal detachment, and the depolymerization of the hyaluronic acid will stop. Consequently—as demonstrated in the present analyses—we find a somewhat higher hyaluronic acid concentration in cases of more long-standing detachment.

The hypothesis here advanced needs further testing on several points. If it proves possible to apply Mayer and Kull's neutralisation of hyaluronidase, successfully carried out in the skin with antihistamines, to the problem of retinal detachment we may thereby have a chance of supplementing with a causal therapy our current operative treatment, the results of which, as is well-known, are of limited value and merely symptomatic.

Whether we may be justified in drawing certain conclusions with regard to the result of the surgical diathermy treatment on the basis of estimation of the hyaluronic acid concentration in the subretinal fluid is a question which cannot yet be definitely answered. It will be discussed further in a future paper.

In cases of retinal detachment, where an underlying malignant melanoma in the choroid is suspected, we may sometimes fail to reach a definite clinical diagnosis by our present diagnostic aids. The present hyaluronic acid investigations suggest that, by analysis of subretinal fluid procurable by simple test puncture, we have obtained a new differential-diagnostic aid for classification of the uncertain cases where malignant tumour is suspected, because hyaluronic acid is not present in the subretinal fluid in cases of malignant melanoma.

Absence of hyaluronidase in the two cases of malignant melanoma does not necessarily exclude the fact that hyaluronidase may have been present at previous stages of the tumour proliferation, as is known from other malignant tumour proliferations. That the violently metastasizing melanomata may be supposed at a certain stage to possess a large hyaluronidase activity is a possibility which requires further investigation.

**Summary and Conclusions**

The main features of our present knowledge concerning the nature of the subretinal fluid in retinal detachment, the vitreous body, and the recent biological discoveries of hyaluronic acid and
Hyaluronic Acid in Subretinal Fluid

Hyaluronidase are recapitulated. This is followed by a report on present investigations into hyaluronic acid and hyaluronidase in the subretinal fluid in retinal detachments, partly primary with ruptures and partly secondary as a consequence of malignant choroidal melanoma.

Hyaluronic acid and hyaluronidase have been estimated viscosimetrically. In all cases of detachment with retinal ruptures the subretinal fluid contained a considerable amount of hyaluronic acid, which, on the other hand, was absent where the detachment was secondary to choroidal melanoma. Hyaluronidase was demonstrated in none of the cases.

These observations have prompted a new hypothesis concerning the pathogenesis of retinal detachment. The development is now conceived to take place gradually by a primary, vascular retinal ischaemia producing cystoid degeneration with rupture formation, and associated with partial liquefaction of the vitreous body. The liquefaction is caused by local liberation of hyaluronidase, which in turn produces partial depolymerisation of the hyaluronic acid in the vitreous body.

Tests for hyaluronic acid in the subretinal fluid may become of differential diagnostic importance in difficult cases of malignant melanoma with extensive secondary retinal detachment and small primary tumour.

Hyaluronic acid analyses may become prognostically directive for the diathermal treatment of retinal detachment. Since hyaluronidase may be inactivated by antihistamines (Mayer and Kull) the possibility of a supplementary causal treatment with these substances is suggested.

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CHOROIDAL SARCOMA WITH METASTASIS IN THE OPPOSITE ORBIT*

BY

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The history here recorded is that of a woman who, ten years after enucleation of one eye for choroidal sarcoma, developed an encapsulated metastasis in the opposite orbit.

HISTORY

In February, 1938, a lady, aged 59 years, attended the Royal Westminster Ophthalmic Hospital because the right eye had become red and painful. The sight had been failing for a year in this eye, and was only perception of light. She was found to have glaucoma secondary to a large choroidal sarcoma, and the eye was removed (see Fig. 1). Microscopic section confirmed the diagnosis (see Fig. 2).

At this time her left eye was normal, and its corrected vision 6/6. She continued to attend the hospital, but no recurrences arose, and she remained in normal health. Apart from the periodical replacement of her glass eye, nothing unusual happened for nine years.

April, 1947. The patient had an attack of iridocyclitis in the left eye which cleared up completely in one month.

May, 1948. It was found that, whereas the patient had worn a correction of -2-0 sph./+0-5 cyl. at 90° with which she saw 6/6, her refraction had now changed, and she achieved normal vision with a +0-5 cyl. at 90°. While this drop of 2 dioptries of myopia was noted, there was nothing to account for it, and the patient had no complaint, being pleased that her vision had so improved.

October, 1948. The patient noticed that the left eye appeared to be coming forward, and reported to hospital. The proptosis was straight forward, and there was no limitation of movement. This proptosis was variable, and in the following month seemed less marked. X-rays of the orbit revealed no bony changes and the fundus and vision remained normal.

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