EFFECT OF CORTISONE ON RHEUMATOID NODULES OF THE SCLERA (SCLEROMALACIA PERFORANS)*†

BY

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Van der Hoeve (1931), basing his observations on two cases, drew attention to a condition characterized by the spontaneous appearance of scleral perforations, which he named scleromalacia perforans. A somewhat similar case had previously been described by Holthouse (1893), and Kuhnt (1912) reported a case of scleral perforation associated with hydroa vacciniforme. Under the term scleritis necroticans Rochat (1933) described two further cases but he was later willing to accept the earlier designation. Van der Hoeve (1934) reviewed his original material with that of Rochat and referred to two additional cases. He noted that the disease was bilateral in most patients and began in the anterior sclera with yellow or greyish subconjunctival nodules, associated with a gradually developing scleral necrosis, progressing to perforation with exposure of the uvea. Three of these cases presented a history of pre-existing chronic articular disease of an ankylosing type and this feature he associated with the ocular condition to form a distinct syndrome. Following upon van der Hoeve's recognition of this disease-entity, further cases were reported by Eber (1934), Wojno (1935), Kiehle (1937), Cast (1937), Soriano and Riva (1937), and Urrets Zavalia and others (1937).

Verhoeff and King (1938) reviewed fourteen cases which they had at that time been able to trace in the literature and described a fifteenth in which the eye had been enucleated, thus providing the first complete histological report of the condition. They were able to confirm the features of the ocular manifestations as originally described and emphasized the association with rheumatoid arthritis. They were the first to point out that the histological changes in the scleral nodules were essentially similar to those of the subcutaneous nodules of rheumatoid arthritis, and they suggested that the reaction might be due to the deposition of a chemical substance arising in the course of some metabolic disturbance; the deposition of urates in gout was an analogous process. Indeed it is interesting to note that more recently van der Hoeve (1948) has advanced the theory that scleromalacia perforans arises from a disturbance of the lipoid and cholesterol metabolism, and that he associates it with the group of diseases which includes Hand-Schüller-Christian disease, Niemann-Pick disease, Tay-Sachs disease, and xanthomatosis.

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Since the report of Verhoeff and King (1938), numerous cases, reviewed by François (1951), have been added to the literature, and it has become apparent, as pointed out by Franceschetti and Bischler (1950) and by Malbrán and Manzitti (1951), that there is a danger of confusing scleromalacia perforans with a number of other conditions, which are essentially different although clinically similar in some respects. However, in typical cases of scleromalacia perforans there is clearly an aetiological relationship between the scleral lesions and the co-existing rheumatoid arthritis, and we are in agreement with those who believe that, until the exact cause of the condition is known, it is more appropriate to regard scleromalacia as a manifestation of rheumatoid arthritis, thus belonging to the group of collagen diseases. This term was originally proposed by Klemperer, Pollack, and Baehr (1942) to designate a number of acute and chronic maladies of unknown aetiology in which there are widespread alterations of connective tissue, particularly in the extra-cellular substance. The category includes rheumatic fever, rheumatoid arthritis, polyarteritis, acute lupus erythematosus, generalized scleroderma, and dermatomyositis. The fibrinoid collagen change which is such a striking feature of scleromalacia, is such as would be expected in a collagen disease affecting a tissue with such a high collagen content as the sclera. This point, together with further arguments for regarding the pathological changes in scleromalacia as identical to those arising in other tissues in the collagen diseases, has been particularly well presented by Christensen (1951), Stillerman (1951), and Swan (1951).

Although the inclusion of apparently unrelated disorders within the group of the collagen diseases does not necessarily imply an aetiological relationship between them, their development is believed to be connected with immune processes and the noxious effects of hypersensitivity. The beneficial effects of ACTH and cortisone in such states have been amply demonstrated, and it appears that they may control the disease process by suppressing the inflammatory reaction resulting from antigen-antibody union in the tissues (Dougherty, 1951). On the other hand, Klemperer (1950) has suggested that there may be a primary abnormality in the chemical constitution of the ground substance, and since we now know that the formation of collagens tissue and ground substance is to some extent subject to the influence of the adrenal cortex and other hormones (Russell, 1950), it is reasonable to suppose that disease in this system might arise from hormonal imbalances, which ACTH or cortisone therapy is able to rectify. Whatever the mode of action of such treatment, it would obviously be of interest to determine its effect upon the course of scleromalacia perforans, and the purpose of this paper is to report the treatment of such a case with cortisone, the remarkable alterations in the ocular lesions being described in detail. The subsequent death of the patient by providing an eye for pathological examination permitted comparison of the histological appearances with those of eyes from other patients in whom such treatment had not been possible.
Case Report

History.—A male patient aged 41 years, suffering from advanced rheumatoid arthritis of some 8 years' duration, was first seen by one of us (H. E. H.) on March 14, 1950, at the request of Dr. E. T. D. Fletcher. At that time the condition of scleromalacia perforans was fully established in both eyes. A history of bilateral scleritis 9 months previously and of a very recent appearance of scleral perforations was later obtained from Mr. J. E. M. Ayoub, assistant ophthalmic surgeon to the London Hospital.

Examination.—A number of yellowish episcleral nodules, about 3-4 mm. in diameter, and scleral perforations covered by intact conjunctiva through which the bluish-black uvea could be seen bulging slightly, were present anteriorly in both eyes. In some of the perforations yellowish-white sloughs of scleral tissue were to be seen, but no indications of an inflammatory cause were present, the media being entirely clear. There was, however, slight conjunctival injection and photophobia. The appearance is shown in Fig. 1.

There was no indication of active tuberculosis; uric acid/creatinine ratio varied from 1.5 to 0.712/1; no significant alteration of blood cholesterol levels.

Therapy.—Treatment at first was purely symptomatic with atropine and local irrigations, and in general the lesions were seen to progress; further episcleral nodules appeared, disintegrated, and were followed by new scleral perforations. More scleral sloughs formed and those already present increased in size. Later, however (May 30, 1950), there were signs of an attempt at scleral regeneration in the formation of a very thin film of whitish tissue beneath the conjunctiva in the perforated areas. Under a hand lens it showed a fine fibrillar structure, and was apparently composed of fibrous tissue.

Cortisone was first begun (June 23, 1950) as hourly eye drops, a 1:5 dilution of cortisone acetate suspension in normal saline being employed. Some symp-
matic improvement was experienced at once as a reduction of photophobia, and the conjunctival injection was reduced. During the 3 weeks of this administration there was a shrinking and flattening of the episcleral nodules with an increased formation of new fibrous tissue over several of the perforations, although a further new scleral
perforation appeared in one eye. Systemic treatment later became possible (July 14, 1950, to July 22, 1950) at a dosage of 100 mg. daily, and the healing process continued so that at the end of the week several of the perforations showed quite firm coverings of new scleral tissue. Figs 2 and 3 show the appearance of the eyes a month later, on August 14, 1950, and Fig. 4 shows a large temporal perforation of the left eye at the same time. Covering with new scleral tissue is almost complete, but the intermediate stage with a fine fibrillar appearance is still clearly seen in one area.

After the withdrawal of cortisone the conjunctival injection and photophobia returned within a day or so, but they were again abolished when administration was recommenced (September 15, 1950) with hourly cortisone drops and 100 mg. cortisone intramuscularly for 8 days. The essential ocular lesions showed a steady improvement with increasing scleral regeneration, but none of them completely healed and some showed little further change until the condition began to deteriorate in mid-December; fresh perforations and episcleral nodules appeared in both eyes (December 28, 1950), shortly before death occurred from septic pericarditis on January 12, 1951. Cortisone drops had been administered, 4-hourly from October 29, 1950 until one week before death. The right eye was obtained at post mortem for histological examination.

Histopathology of Right Eye.—Macroscopical examination showed a number of subconjunctival nodules in the upper temporal quadrant and irregular ulcerations in the anterior part of the sclera in the upper nasal quadrant of the eye. Scleral perforation had occurred at one point in an ulcerated area. Oblique sections were cut in order to demonstrate both types of lesion.

Sections.—An extensive ulceration of the nasal sclera is present immediately behind the region of the ora serrata. There is a deep necrosis of the scleral lamellae leaving only a thin irregular lamina of chronically infiltrated and partially necrotic sclerosed...
tissue overlying the choroid. The lips of the ulcer are infiltrated by chronic inflammatory cells among which a few giant cells are visible, and the crater is covered by a thin membrane of newly formed fibroblastic tissue (Fig. 5). The posterior walls of the ulcer cavity also show evidence of incipient fibroblastic proliferation. Areas of necrosis are present in the chronically infiltrated episclera behind the zone of ulceration, and the medial rectus muscle shows a marked infiltration by chronic inflammatory cells. Anterior to the ulcer, both the infiltrated sclera and the scarred peripheral cornea are markedly thinned. The anterior sclera on the temporal side of the globe is also chronically infiltrated and attenuated, and diffuse hyalinization of the stromal lamellae has occurred. Sections through the nodules in the upper temporal region show them to be situated in the outer layers of the sclera and in the tendinous expansion of the insertion of the external rectus muscle. They consist of masses of hyalinized and completely degenerate scleral and tendon fibres surrounded by a pale, clearly-defined zone of palisading fibroblasts which in turn is surrounded with a zone of chronic inflammatory cells, in which plasma cells and lymphocytes predominate while eosinophils and polymorphonuclears are notably few in number. A few nodules are present in the posterior half of the sclera on the nasal side (a most unusual feature in scleromalacia).

There is an early necrosis of the choroid underlying the ulcerated area where the differentiation between choroid and sclera has been almost completely obliterated but the retinal pigment layer is still intact. Scattered chronic inflammatory cells are present in the sclerosed iris and ciliary body, the pars plana of which shows marked atrophic changes. The lens is cataractous. The anterior choroid is atrophic, whilst posteriorly there is an advanced choroidal sclerosis associated with a chronic inflammatory infiltration in which one or two focal aggregations of pus cells are present. The retina shows some oedema in the nerve fibre layer, but the optic nerve shows no particular abnormality. The histological picture is that of scleromalacia perforans.

The sections described above were compared with histological preparations from six other cases of scleromalacia perforans not treated with cortisone, and areas showing approximately the same stage of the disease were selected for comparison. The following points were noted:

(a) The inflammatory reaction in the untreated cases was considerably more

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**Fig. 5.**—Ulcerated area in scleromalacia perforans treated with cortisone. Although there is still considerable necrosis, fibroblasts are proliferating in the walls of the ulcer cavity, and the crater is covered by a thin membrane of newly-formed fibroblastic tissue. A few giant cells may be seen. Haematoxylin and eosin. × 50.
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marked and contained large numbers of polymorphonuclears and eosinophils, whereas these cells were almost absent in the treated case.

(b) At the abrupt boundary between the fibrinoid material and the infiltrated sclera the untreated cases showed only moderate palisade formation and there was little fibroblastic proliferation (Fig. 6). In the treated case, however, there was a marked fibroblastic regeneration over the ulcerated areas (Fig. 5) and the palisade arrangement of the cells around the necrotic foci was more definite and more uniformly orientated. See Fig. 7 (above) and Fig. 8 (overleaf). Cortisone had not only inhibited the inflammatory reaction, but had also, to some extent, promoted repair processes.

Fig. 6.—Nodular area in scleromalacia perforans not treated with cortisone. The inflammatory reaction contains neutrophilic and eosinophilic polymorphonuclears. Around the area of fibrinoid necrosis there is but little attempt at palisade formation. Cf. Fig. 7. Haematoxylin and eosin. × 90.

Fig. 7.—Nodular area in scleromalacia perforans treated with cortisone. The inflammatory infiltration is mononuclear and there is a marked palisading of cells around the necrotic focus, in which some calcification has occurred. Cf. Fig. 6. Haematoxylin and eosin. × 70.
(c) There was no evidence of cytoplasmic vacuolization or of cyst formation: the giant cells were somewhat more numerous in the treated case.

**Discussion**

In summary, our investigation shows that cortisone is able to exert a beneficial effect upon the lesions of scleromalacia perforans, as evidenced by a shrinking of the nodules and by scleral regeneration in the necrotic areas;

![Fig. 8.—High-power view of Fig. 7, note marked palisading of cells and calcifying necrotic area. Such a high degree of palisading was not seen in six cases not treated with cortisone. Haematoxylin and eosin. × 120.](image)

the histological examination indicates that these changes are due to an inhibition of the inflammatory reaction, particularly with regard to the neutrophilic and eosinophilic polymorphonuclear infiltration, and to a regeneration of fibroblasts.

It is interesting that Mundy and others (1951) came to almost identical conclusions from a similar study in a closely related condition. They performed three scleral biopsies on a case of rheumatoid arthritis with bilateral episcleral nodules, one being taken before and two during systemic treatment with cortisone. The histology was similar to that of scleromalacia. The nodules gradually decreased in size and by the fourteenth day of treatment were barely visible. Although these workers were unable to correlate this dramatic clinical improvement with a comparable degree of histological change, they noted that the cellular infiltration became predominantly mononuclear owing to a reduction in the numbers of neutrophilic and eosinophilic polymorphonuclears. The third biopsy showed proliferation of fibrocytes which, as in our case, tended to palisade around the fibrinoid necrosis.

A very complete study of the histological changes in rheumatoid nodules, both in the sclera and subcutaneously, has been carried out by Fienberg and Colpoys (1951). The occurrence of numerous rheumatoid nodules of the
sclera in a patient with advanced rheumatoid arthritis offered them the rare opportunity of removing such nodules at various intervals before and during the course of treatment with cortisone. It was also possible to study a scleral nodule, clinically 24 hours old, which appeared 32 days after treatment stopped. In addition, one half of a subcutaneous nodule of the elbow was removed from the same patient before treatment and the other half after cessation of treatment. The patient subsequently died and the recurrent scleral nodules and visceral rheumatoid nodules became available for study. Thus the investigation of Feinberg and Colpoys, as also that of Mundy and others, was superior to ours, in that they could compare the histological effects of cortisone upon the nodules with untreated lesions from the same patients.

To some extent the findings of Feinberg and Colpoys agree with ours and with those of Mundy and others, for they also observed an inhibition of the inflammatory reaction with diminished exudation and the development of a mononuclear reaction with a disappearance of eosinophils (which incidentally reappeared after cessation of treatment). During the course of treatment, they also noted the appearance of plump, elongated, rounded fibroblasts and an increase in the number of giant cells. Their report differs from ours in that they observed cytoplasmic vacuolization, and liquefaction in the foci of necrosis with central cyst formation, changes not seen in our sections.

More surprising was their finding that cortisone apparently produced a disorganization of the polarity of the palisaded cell layer, whereas our own evidence points in the opposite direction. In our preparations there was no question that the marked palisading and uniform orientation of the cells around the necrotic foci were considerably greater than in cases not treated with cortisone. No doubt further experience with cortisone in scleromalacia will elucidate this point; meanwhile such disparities in the histological findings may to some extent be explained by the fact that our own material is not strictly comparable with that of Feinberg and Colpoys. In their case, no perforations were present which had not advanced beyond the earlier nodular stage, and their dosage of cortisone was larger than ours. Furthermore, it is to be remembered that the details of disease reactions vary from case to case as do also individual responses to cortisone therapy. Indeed, several workers have found no histological alterations in rheumatoid nodules after ACTH or cortisone therapy (McEwen, 1950; Bauer, 1950; Ragan and others, 1949; Spain and Roth, 1951).

However, upon the three important features of the effect of cortisone in scleromalacia—namely, regression of nodules, inhibition of inflammatory reaction and fibroblastic regeneration—we all appear to be in agreement. That cortisone should inhibit the inflammatory reaction in these scleral lesions is exactly what one would expect for there is now considerable evidence to this effect in the literature (Duke-Elder and Ashton, 1951). It is thought that cortisone exerts this influence by preventing an increase in capillary permeability, which is an essential component of the vascular
phenomena in the inflammatory process. It is not, therefore, surprising to find a reduction in polymorphonuclear infiltration in the case treated with cortisone, for, to mention only one point, the diapedesis of these cells would obviously be obstructed; the fact that the mononuclear infiltration was but little affected suggests either that the cells appeared before treatment and had persisted in the tissues, or that they had migrated from adjacent lymphoid follicles. With regard to the marked reduction of eosinophils in the tissues, three possible explanations present themselves: cortisone eosinopenia; prevention of diapedesis; and modification of the hypersensitive state.

The fibroblastic regeneration in the case treated with cortisone is less easy to understand, for it is well known that cortisone depresses fibroblastic activity. However, this action is by no means absolute for it is related to the amount of cortisone given (Ashton and Cook, 1951); nor should it be forgotten that other factors tending to encourage fibroblastic regeneration are at work. Thus the ability of cortisone to damp down the reactivity of mesenchymal tissue is clearly of importance in controlling further fibrinoid changes in the connective tissue, thereby promoting conditions more favourable to repair processes. That ACTH and cortisone are able to inhibit fibroblastic repair in subcutaneous rheumatic nodules was shown by Hunt and Blanchard (1951); though these authors found an inhibition of fibrinoid alteration, there was a striking reduction in the proliferation of mesenchymal cells in the zone surrounding the central areas of necrosis. The fibrous regeneration was well marked in our case, despite the fact that complete healing was never obtained, but the dosage of cortisone administered was half that given by Hunt and Blanchard. It would appear, therefore, that cortisone, while suppressing the disease process, simultaneously inhibits repair, and the extent to which fibrosis eventually occurs depends upon the outcome of these opposing forces, which must obviously be related to the severity of the disease and to the dose of cortisone administered. These facts may explain the apparently contradictory evidence in the literature dealing with the effects of cortisone upon rheumatic lesions.

As is well known, spontaneous healing not infrequently occurs in rheumatoid nodules, and a case in which scleral nodules healed in such a way was described by Verhoeff and King (1938). A case reported by Friedenwald (1921) may have been of this nature. Feinberg and Colpoys (1951) compared the histological changes in their treated case with those found in eight rheumatoid nodules undergoing spontaneous involution, and concluded that cortisone induces an acceleration of involution and hastens regression by preventing the occurrence of further activity. While our findings lead us to similar conclusions, some modification of the statement of these last workers is required to explain the failure of cortisone to produce complete involution in all cases. It would probably be more accurate to say that, providing the disease process is not too severe or too advanced, cortisone may prevent further activity and so create suitable conditions for fibrous regeneration, a
process which, being inhibited in proportion to the concentration of cortisone present, will depend in extent upon the quantity of hormone administered. When sufficient cases of scleromalacia perforans have been treated with cortisone, it may become more apparent that this dual effect should be taken into account in deciding upon dosage.

Summary

(1) The literature dealing with scleromalacia perforans is briefly reviewed. It is believed that this condition should be regarded as belonging to the group of collagen diseases, and would be better named "rheumatoid nodules of the sclera".

(2) A case of scleromalacia perforans treated with cortisone is described, and the post mortem histological appearances of one eye are compared with eyes from six patients in whom such treatment had not been possible.

(3) Clinically, the administration of cortisone gave rise to a shrinking and flattening of the nodules with an acceleration of healing. There was considerable covering of the ulcerated areas with new fibrous tissue but none of the lesions healed completely.

(4) Histologically, the eye sections, when compared with those from the untreated cases, showed a marked inhibition of the inflammatory reaction, particularly with regard to neutrophilic and eosinophilic polymorphonuclear infiltration. The case treated with cortisone showed a much more marked fibroblastic regeneration, and the palisading arrangement around the areas of fibrinoid necrosis was more definite and more uniformly orientated.

(5) The findings are discussed in relation to other published reports, and it is concluded that in scleromalacia perforans cortisone prevents further activity and thus creates suitable conditions for fibrous regeneration, but that the regenerative process is inhibited in proportion to the concentration of cortisone present. With further experience it may become more apparent that this dual effect should be taken into account in deciding upon dosage.

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REFERENCES