ACTION OF CORTISONE ON TISSUE REACTIONS OF INFLAMMATION AND REPAIR WITH SPECIAL REFERENCE TO THE EYE

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It has already been shown in the two previous articles in this issue of the Journal that the clinical effects of cortisone and ACTH have excited much interest and a very extensive literature; the reports dealing with their effects upon the fundamental reactions of inflammation and repair, however, are as yet relatively few in number and there is still considerable disagreement over some of the more important problems. This is unfortunate and to some extent illogical, but it is only to be expected that agents which can exert an effect so dramatic upon many ocular diseases should be exploited clinically to the fullest possible extent at the earliest moment, even although the theoretical foundation for their action remains obscure.

Only a few workers in ophthalmology have hitherto pursued their studies into the field of experimental pathology (Woods, 1950; Woods and Wood, 1950; Biegel, 1951; Leopold and others, 1951; Bourquin, 1951). Such investigations could well be of more than local importance, for the relative isolation of the eye and the facilities it provides for the study of the microscopical tissue-changes of disease, so readily discernible both in the living animal and in histological preparations, make this organ a unique sphere for investigation. In the papers which follow in this issue, some initial studies on the effect of cortisone on inflammatory processes as seen in the eye are therefore reported. In the present paper these are correlated with cognate work in the general literature on the action of ACTH and cortisone upon the inflammatory process, considering it in relation to the two essential components of the defensive and reparative reactions. The sub-divisions we have chosen represent some of the stages in these reactions, but the classification is not entirely satisfactory, because, owing to the lack of published experimental data, some details, such as the effect of cortisone on the margination and diapedesis of polymorphonuclears and phagocytosis, etc., have had to be omitted.
The literature will, therefore, be reviewed under the following headings:

(a) capillary permeability,
(b) inflammatory exudation,
(c) cellular infiltration and the formation of granulation tissue,
(d) the formation of connective tissue,
(e) new vessel formation,
(f) epithelial and endothelial regeneration.

(a) Action of Cortisone on Capillary Permeability

An increased permeability of the capillaries is an accompaniment of all inflammatory processes, and it constitutes an important feature of the exudative phases of the inflammatory reaction which in a previous paper we have seen to be blocked by the administration of cortisone, whether administered topically or systemically. An enquiry into the effect of cortisone on the permeability of the normal and abnormal capillary wall is therefore of importance.

The permeability of the capillaries of the skin of the rabbit has been investigated by Menkin (1951a), who found no change after the injection of ACTH or cortisone acetate when the latter was used suspended in saline free from any alcohol or vehicle. It is to be noted, however, that he found an increased permeability at the site of injection when the commercial suspension of cortisone was employed—a circumstance which should be taken into account when the action of this preparation is being investigated experimentally and clinically.

The eye lends itself ideally to such a study, for the permeability of the capillary walls can be assessed with considerable accuracy by the optical measurement of the appearance of fluorescein in the aqueous humour in the anterior chamber after this dye has been injected intravenously. Owing to the relative impermeability of the ocular capillaries, the transfer of fluorescein across the blood-aqueous barrier is a measure of the permeability of the capillary walls rather than of the rate of blood-flow, a factor which is of importance in other tissues of the body. Leopold and his co-workers (1951) found no significant difference in the rate of appearance of this dye in the aqueous humour of normal rabbits without cortisone and in that of animals after the exhibition of cortisone, whether instilled as drops, injected subconjunctivally, or introduced into the anterior chamber. This finding has been confirmed by the work of Cook and MacDonald (1951), for, using the technique standardized by Amsler and Huber (1946), they have shown that the permeability of the blood-aqueous barrier to this dye in the normal human eye is not affected by the local or systemic administration of this hormone.
PATHOLOGICAL ACTION OF CORTISONE

It would thus appear that cortisone has no significant effect upon the permeability of the normal capillary, but this does not imply that it may not exert an influence upon abnormal vessels. Indeed, there is evidence to suggest that it may act by restoring a pathologically increased capillary permeability to normal.

There is little to be learned from the general literature on this subject. Such a reduction at the site of inflammation was demonstrated by Armstrong and Irons (1951) to follow the administration of ACTH in a patient with scleroderma: before the administration of ACTH the protein content of the oedematous fluid in the vesicles of the skin of the lower extremities was 2.5 per cent., a value which fell after the administration of ACTH to 0.5 per cent. It is true that Schirmer (1950) reported a patient with arthritis who developed capillary fragility with numerous petechiae after the administration of cortisone, a complication which disappeared completely when cortisone was discontinued; but this result was exceptional and may have had other explanations; it can probably be reasonably disregarded in considering capillary permeability.

In the eye, the evidence is more unequivocal, for the work of Cook and MacDonald (1951) has shown that, while the capillary permeability in the human eye, as measured by the passage of fluorescein into the anterior chamber, is increased in inflammatory conditions, the administration of cortisone, either locally (by the instillation of drops or subconjunctival injection) or parenterally, reduces the permeability dramatically to the normal level. It is noteworthy that this effect is temporary and that an increase in permeability rapidly returns, even although a relapse of the inflammatory symptoms is not clinically evident.

It is interesting that a definite increase in capillary resistance, as measured by the negative pressure method, was demonstrated by Robson and Duthie (1950) after the administration of ACTH in six cases of rheumatoid arthritis, two cases of spondylitis ankylopoietica, two cases of lupus erythematosus, and two cases of thrombocytopenic purpura, diseases in which the capillaries are generally believed to be abnormal. They considered that these changes were due to adreno-cortical activity.

Although cortisone thus seems to have no influence on the permeability of the normal capillary, it appears to be able to reduce to normal the increased permeability characteristic of inflammation. This is a finding that cannot be without significance. This decrease of the abnormal permeability would obviously act in the direction of inhibiting the exudative manifestations of inflammation and of interfering with the demand for fibroblastic and other reparative activities for increased nutritional supplies. The experimental work so far completed does not indicate whether this decrease in permeability occurs as a primary event, or whether it is a concomitant or a consequence of changes at another level in the reactions of the tissues to irritation: the elucidation of this question must await further enquiry.
The mechanism of the alterations in capillary permeability in inflammatory conditions is not yet clear. It has been known for some time that its increase is determined, in part at any rate, by the presence of leukotaxine, a nitrogenous substance present in inflammatory exudates (Menkin, 1940, etc.). Recent evidence points to the presence of other factors which affect the permeability of the capillaries similarly, but, at least as far as leukotaxine is concerned, it has been demonstrated that adrenal cortex extract or cortisone inhibits this action (Menkin, 1951b). It is also known that the permeability of capillaries and connective tissue is increased by hyaluronidase administered either locally or intravenously (Duran-Reynals, 1942; Opsahl, 1949; Elster and others, 1949; Seifter and others, 1949; Duran-Reynals and others, 1950; Sprunt, 1950); this increase in permeability has been found to be suppressed by cortisone whether given locally or systemically (Opsahl, 1949; Seifter and others, 1949; Shuman and Finestone, 1950; Benditt and others, 1950). This action can be demonstrated locally by studying both the intradermal spreading reaction of Indian ink (Opsahl, 1949) and the leakage of dyes such as Evans or trypan blue from the blood stream into the tissues (Benditt and others, 1950; Armstrong and Irons, 1951). It is not known whether the hormone acts on the tissue cells or on their ground substance directly or by some intermediate reaction, or whether it interferes with the spreading factor, hyaluronidase. In this regard the unusually large amount of hyaluronidase in the eye may be of importance, and it is interesting that Lepri and Montanari (1951) found a significant diminution of hyaluronidase in the aqueous humour after the systemic injection of ACTH in animals.

It is also interesting that Seifter and his co-authors (1949) found that hyaluronidase or desoxycorticosterone acetate (DOCA) produces a large increase in the permeability of the synovial membrane of joints, an increase antagonized by steroids of the cortisone type. Somewhat parallel findings have been noted in the eye by Pentini and Fornaro (1950): DOCA was found to produce an increase of glucose in the aqueous humour of rabbits and a decrease of this substance in the lens, changes which were inhibited, more or less completely, by the injection of ACTH. It would seem that these steroid substances have a reciprocal influence on the permeability of such membranes as the synovial membrane and the blood-aqueous barrier.

(b) Action of Cortisone on Exudative Phenomena

The extraordinary efficacy of cortisone in the control of the exudative phenomena of inflammation as seen in clinical cases would lead to the expectation that such an inhibition could be readily demonstrated pathologically or experimentally. It is curious that little work has been done directly on this problem in general pathology. Spain and others (1950a) studied the healing of wounds in mice, and noted, on examination 24 hours after wounding, that there was an almost complete lack of the formation of exudate and fibrin in the cortisone-treated group; these results were confirmed by Michael and Whorton (1951) in skin lesions produced in rabbits.
by croton oil and scratches. It is interesting that, in another series of experiments, Spain and his co-workers (1950b) found that cortisone had no effect on the early formation of acute inflammatory exudates in response to intracutaneous injections of turpentine; it may well have been that the toxic action of the turpentine injured the vessels too severely for cortisone to be effective in restoring the normal permeability, and that this gradation in response finds a parallel in the partial control of very severe inflammations which we have seen in a previous paper to occur clinically in diseases of the eye (Duke-Elder, 1951).

So far as experimental work on the eye is concerned, Biegel (1951) found that cortisone inhibited the formation of plasmoid aqueous and fibrinous collections in the anterior chamber in cases of horse-serum uveitis in rabbits. This finding has been supplemented by the observations of Ashton and Cook (1951) in their experiments on the healing of incised wounds in rabbits' cornea described in this issue (p. 708). Cortisone, in the doses they used, was found to have a mild but definite inhibitory effect on the formation of the fibrinoid coagulum in the wounds. It is obvious that many of the beneficial effects of ACTH and cortisone in the treatment of ocular disease may be attributed to this blockage of the exudative tissue-reaction, which in the eye may have catastrophic results.

(c) Action of Cortisone on Cellular Infiltration and on the Formation of Granulation Tissue

Several investigators have demonstrated the marked inhibitory effect of cortisone on experimentally produced allergic and traumatic inflammations. In the skin, wherein observations are relatively easy, this is exemplified in the work of Shwartzman and others (1950), who showed that the severe local reaction produced in rabbits by the intradermal injection of a meningococcal culture filtrate, followed 24 hours later by the intravenous injection of a large provocative dose of the material, could be inhibited in a large majority of cases (although not invariably) by a prior intramuscular injection of cortisone. These findings have been corroborated histologically in allied allergic and traumatic inflammations by Dougherty and Schneebeli (1950), who deduced that the inhibition of the inflammatory response occurred without interference with the antibody-antigen reaction, and by Armstrong and Irons (1951), who found that the reduction of cellular exudate involved polymorphonuclears, leucocytes, round cells, and lymphocytes. Similarly, the study of the healing of cutaneous wounds in mice and rabbits has shown that cortisone has brought about a retardation in the formation of granulation tissue (Baker and Whitaker, 1950, and Shapiro and others, 1951, in the rat; Spain and others, 1950a, in mice; Plotz and others, 1950, and Ragan and others, 1950, in rabbits' ears), although
no effect has been demonstrated on already existing granulation tissue if the hormone has been administered during the later stages of healing (Spain and others, 1950b).

In human diseases, these experimental findings are paralleled by the observations of Shick and others (1950), who found in two cases of periarteritis nodosa, wherein the presence of arteritis had been demonstrated on biopsy, that all histological signs of inflammation disappeared after treatment with cortisone, within three weeks in the first case and within three months in the second; at this stage histological examination of multiple sections from many organs failed to reveal a vessel which was the site of active inflammation. A similar decrease of the cellular infiltration of the diseased portions of the liver in infective hepatitis after the administration of cortisone was demonstrated by Hanger and Collins (1950), but the active necrosis of parenchymal cells was not abolished. Finally, a retardation of the formation of granulation tissue in wounds of the skin in man has been observed by Creditor and others (1950).

Experimental work on the eye in this field has not been extensive but it has pointed to the same conclusion. In the eyes of experimental rabbits, Woods (1950) and Woods and Wood (1950) have found that cortisone and ACTH effectively block the inflammatory phase of the hypersensitive reaction in tuberculin-sensitive rabbits. Similarly, the inflammatory reaction secondary to the injection of glycerin or jequirity (Woods, 1950) or talc (Bourquin, 1951) into the anterior chamber has been shown to be controlled. The inhibitory effect of cortisone on cellular infiltration was particularly well shown by Biegel (1951) in the experimental production of horse-serum uveitis in rabbits, and the photographs of sections of the uvea in his paper clearly demonstrate the relative acellularity in the series under treatment with cortisone. This work has been taken a step further in a subsequent paper in this Journal, wherein it is shown that cortisone exerts a similar reduction in the cellular inflammatory reaction in incised wounds in the cornea of the rabbit (Ashton and Cook, 1951).

There appears, therefore, to be general agreement that cortisone inhibits the cellular infiltration associated with inflammation and also the formation of granulation tissue in the healing process in the body generally and also in the eye.

(d) Action of Cortisone on the Formation of Connective Tissue in the Healing Process

The action of cortisone on the formation of connective tissue in the healing of wounds and in inflammatory processes has excited a considerable amount of attention since the observation by Plotz and others (1950a) that there was a marked delay in the healing of spontaneous and incised wounds in patients under treatment with cortisone and ACTH.
PATHOLOGICAL ACTION OF CORTISONE

Several techniques have been employed, most of which have been concerned with the readily accessible wounds of the skin. It is interesting that Castor and Baker (1950) applied cortisone to the non-traumatized skin of rats and found that the histological structure in the treated area was modified; the thickness of the dermis was reduced, apparently because of a loss of substance from the collagenous fibres, while fibroblasts and other cells of the dermal connective tissue were fewer in number in the treated regions. Observations on the healing of skin wounds in animals, including wounds of the ears of rabbits, have shown that in the cortisone-treated animals fibroblastic activity is depressed, new fibroblasts are few, and there is much less ground substance as determined by staining with toluidene blue (Ragan and others, 1950; Plotz and others, 1950; Spain and others, 1950; Baxter and others, 1951a; Cavallero and others, 1951).

Observations on the healing of wounds of the skin in man have been contradictory. On the one hand, Creditor and others (1950), treating two patients with ACTH, took elliptical skin biopsies on the first day of therapy and after one week excised the whole area; these showed no evidence of healing of the mesenchymal tissue for, while there was proliferation of the epithelial structures, practically no granulation tissue, leucocytes, fibroblasts, or proliferating blood vessels were seen. The inhibition was of short duration, however, and one week after cessation of the administration of ACTH the wound showed normal healing. On the other hand, Baxter and others (1951b), in patients also treated by ACTH, found that a delay in the healing of skin wounds might or might not occur, and that, if it did occur, the pattern of healing was unaltered.

Any such inhibition, of course, might well be expected to have repercussions which might assume clinical importance. Thus Howes and others (1950), testing the tensile strength of sutured wounds in the skin of rats, found that the bursting strength of the wounds was much greater in control rats than in those treated with cortisone, while in experiments designed to examine the effect of the administration of this hormone upon the healing and growth of skin autografts in rabbits, Billingham and Krohn (1951) found that the primary healing of the grafts was weakened and that their histological re-organization was retarded.

Experimental evidence is also available that a similar inhibition of fibroblastic activity occurs in other organs. Thus a delay in the union of fractures in animals has been demonstrated by Plotz and others (1950) and by Blunt and others (1950), a delay which in the latter authors' experience did not become apparent until about the fourth day. A similar retardation has been found in the healing of wounds of the stomach (Plotz and others, 1950), and an inhibition of the formation of fibroblasts and collagen has been noted in the
tissue-reaction following the injection of turpentine in rats (Taubenhaus and Amromin, 1950) and in the formation of new adhesions in rats injected intraperitoneally with talc (Ducommon and Mach, 1950); in the latter case no effect on established adhesions could be demonstrated. A similar inhibition of the formation of connective tissue in the spleen and lungs of rats infected with Coccidioides immitis and treated with cortisone has been demonstrated by Cavallero and Sala (1951), and of the hepatic fibrosis experimentally induced in rats by the injection of carbon tetrachloride by Aterman (1950) and Cavallero and others (1951). It is interesting that in the latter case fatty degeneration was not affected. In these reactions, ACTH has been noted to have less inhibitory effect than cortisone (Taubenhaus and Amromin, 1950), and other steroid hormones have been found to be inactive in this respect (Plotz and others, 1950).

In the eye less experimental work is available for study. Leopold and others (1951) found that cortisone interfered, although only slightly, with the formation of fibroblasts in the corneal stroma of rabbits after experimental wounds, an effect which these workers observed to be less obvious with the topical application of the hormone than with subconjunctival injections. This suggests that various concentrations of cortisone may have a variable effect on the healing of wounds. Ashton and Cook (1951) have confirmed these findings. These authors found that the inhibition of fibroblastic activity in the cornea was marked but by no means absolute and related to the amount of cortisone given: with moderate doses such as would normally be used therapeutically, adequate healing took place but was less satisfactory than in untreated controls. This experimental observation finds its clinical complement, for the literature shows that ocular operations can be conducted with impunity while the patient is under treatment by cortisone (Duke-Elder, 1951). Ashton and Cook found, however, that if the doses given were large, repair by fibrosis could be almost completely inhibited. It may be of interest that, in their studies on the healing of fractures in the femurs of rabbits, Blunt and others (1950) concluded that the delay in healing caused by cortisone was possibly due to an inhibition in the new formation of blood vessels, but this cannot be held responsible for any retardation of healing in the avascular cornea.

In general, therefore, there is considerable evidence and widespread agreement that cortisone depresses fibroblastic activity and consequently wound healing, both in experimental animals and in man. How the hormone acts in this respect is quite unknown, but that its effect is not a simple and direct inhibition of fibroblastic cells seems indicated by the findings of Steen (1951) that in its presence, unless in very high concentrations indeed, the growth of these cells proceeds actively in tissue culture and mitotic activity is unimpaired.
PATHOLOGICAL ACTION OF CORTISONE

(e) Action of Cortisone on New Vessel Formation

There is a remarkable consensus of opinion among the few experimental workers who have interested themselves in the question whether cortisone exerts a considerable inhibitory influence on the formation of new vessels during the process of inflammation and repair. Thus a depression of this activity in comparison with that in controls was found in wounds of the skin of mice (Spain and others, 1950) and of rabbits (Baxter and others, 1951), and a similar delay in the vascularization of skin-autografts in rabbits was demonstrated by Billingham and Krohn (1951). We have already noted the striking depression observed by Blunt and others (1950) in the formation of new vessels in the healing of fractures in the femurs of cortisone-treated rabbits. The observations of Creditor and others (1950), who found practically no proliferating vessels in skin biopsies taken from two patients treated with ACTH, would seem to indicate that a similar inhibition of new vessel formation occurs in man.

In the eye, vascularization of the cornea as affected by the administration of cortisone has been studied experimentally by Jones and Meyer (1950). These authors found that after the intracorneal injection of sodium hydroxide, vascularization was inhibited when solutions of cortisone were injected subconjunctivally. Leopold and his co-workers (1951), on the other hand, found that cortisone produced no significant diminution of either opacification or vascularization when a concentrated solution of this alkali was applied to the corneal surface or injected intra-lamellarly. It may have been that the violence of the reaction produced by the latter authors was not amenable to amelioration, but the findings of the former have been confirmed by Lister and Greaves (1951) and by Ashton, Cook, and Langham (1951). There is no doubt that, in the case of reactions of reasonable intensity, the vascularization habitually exerted by experimental insults, such as the production of standard corneal burns or the intracameral injection of alloxan, can be controlled by cortisone administered either locally or systemically, although, as in most other activities of this hormone, the control is graded and not absolute.

The rationale of this inhibition of vascularization is not by any means clear, and will probably remain obscure until the mechanism of corneal vascularization in inflammatory processes is understood. It may be that some chemotactic influence exerted by injured tissue upon the limbal capillaries is blocked by cortisone. It may be that the endothelial cells are prevented from responding to such a chemotactic influence by proliferation, a process perhaps parallel with the findings of Ashton and Cook (1951) that in the healing of corneal wounds in rabbits endothelial regeneration was markedly
inhibited by cortisone. Alternatively, some other factor or factors unknown may come into play. Whatever the cause, these experimental findings receive ample clinical corroboration, for one of the most useful and impressive therapeutic actions of cortisone in inflammatory corneal disease is the repression and sometimes even the regression in the evolution of neo-vascularization. In view of the great potential value of this property of cortisone in the treatment of ocular disease, particularly in the suppression of corneal vascularization, further clinical and experimental work is urgently called for to elucidate its mechanism and assess its clinical value.

We have already noted the possibility that cortisone acts as an inhibitor of hyaluronidase. Jones and Meyer (1950) considered that an essential preliminary to the growth of blood vessels into the cornea is a break-down of the corneal polymucosaccharides by hyaluronidase, a suggestion based on the work on this enzyme of Meyer and Chaffee (1940). The subsequent work of Woodin (1950), however, has thrown considerable doubt upon this possibility, for it would appear that hyaluronidase is inactive as a spreading factor in the cornea (of the rabbit and ox), and that the substrate for hyaluronidase is absent from this tissue, an opinion which receives support from the work of Wislocki and others (1947), who found that the metachromatic staining reaction of the cornea with toluidene blue was not abolished by treatment with testicular hyaluronidase.

(j) Action of Cortisone on Epithelial and Endothelial Regeneration

There are few reports of research projects which have had as their main object the study of the effect of cortisone upon the regeneration of epithelium. It is interesting that Castor and Baker (1950), on applying cortisone to the non-traumatized skin of rats for long periods, found that the epidermis became thinner, the growth of hair ceased, the sebaceous glands became smaller, and, in males, the size of the epidermal cells was reduced. The conclusion that cortisone injected systemically or applied locally is a powerful inhibitor of mitosis in the prophase in the epidermis of the adult male mouse would seem to follow from the observations of Green and Ghadially (1951), but it is to be remembered that measurements of mitotic activity and the rate of tissue growth may not necessarily run parallel. Gubner (1951), in drawing attention to the similarity between the therapeutic activity of cortisone and that of the folic acid antagonist, aminopterin, pointed out that, although the locus of their biochemical effects is not the same, both substances are none the less anti-anabolic and tend to inhibit tissue regeneration. He concluded that the therapeutic action of both substances reflects a suppression of both epithelial and mesenchymal activity.

Several authors have referred to epithelial growth in their experiments on the effect of cortisone on the healing of wounds; the
observed, however, are not in agreement. On the one hand, the observations just reviewed would seem to be corroborated by the findings of Howes and others (1950), who reported a diminished epithelialization of wounds in rabbits treated with large doses of cortisone and a slowing of epithelialization with smaller doses, and of Baxter and others (1951a), who found that union by epithelium in skin incisions in rabbits lagged behind that in controls. On the other hand, an opposite finding has been equally substantiated. Spain and others (1950a), in their study of wounds on the backs of forty mice, to which we have previously referred, found that, although there was an arrest of fibroblastic activity in the cortisone-treated group, epithelialization was complete in some wounds. Creditor and others (1950), in a similar study in rabbits, found that, while practically no granulation tissue, leucocytes, fibroblasts, or proliferating new vessels occurred in the wounds of the treated animals, there was a proliferation of the epithelial structures. Finally, Ragan and others (1950), in their study of the healing of defects in rabbits' ears, observed that, in the absence of mesenchymal tissue regeneration, new epithelium proliferated from the edges of the wounds, an observation confirmed by Baxter and others (1951b) in the skin of man.

Only Leopold and his co-workers (1951) have drawn particular attention to this matter as regards the eye; they concluded that epithelial regeneration was delayed by cortisone in standard abrasions of the corneal epithelium. In the experiments of Ashton and Cook (1951) and Lister and Greaves (1951) upon traumatized rabbits' corneae, epithelial regeneration did not appear to be significantly retarded when small doses of cortisone were used, but there seemed to be some inhibition of epithelial growth if the doses were large. It is interesting that our series of clinical cases, reported in the previous paper (p. 672), occasionally showed a retardation in the epithelialization of corneal ulcers, which retained their stain to fluorescein while topical treatment with cortisone was continued, and lost it on the cessation of treatment; but such an effect was sporadic in its incidence. It is clear that further experimental work is required to elucidate the effect, if any, of cortisone upon epithelial growth, but it is equally clear that any such effect is not great. Again, it is to be noted that, whatever the effect in vivo, the growth of epithelial cells proceeds actively in tissue-culture exposed to high concentrations of cortisone (Steen, 1951), an activity comparable to that exhibited by fibroblasts.

The action of cortisone on endothelial regeneration has so far received little attention among experimental investigators, but the significant decrease found by Ashton and Cook (1951) in the normally rapid renewal of the corneal endothelium after wounds in the rabbit cornea may not be without significance.
SUMMARY

A study of the literature and an assessment of the new experimental work carried out in the eye and reported in subsequent papers in this Journal leads to the following tentative conclusions with regard to the action of cortisone in the tissue reactions of inflammation and repair:

1. While no effect is evident on the permeability of the normal capillaries, the increased permeability characteristic of inflammation is significantly lessened.

2. The exudative phenomena associated with inflammation are also inhibited.

3. Cellular infiltration and the formation of granulation tissue are similarly inhibited.

4. The fibroblastic activity associated with tissue repair is diminished with a consequent retardation in the healing of wounds, an effect evident in the avascular cornea.

5. Post-inflammatory neo-vascularization is significantly diminished, an effect well demonstrated in the cornea.

6. There is doubt regarding the effect of cortisone on epithelial regeneration; any influence it may have is small unless the dosage is considerably larger than would be used therapeutically. Endothelial regeneration, in so far as repair of the corneal endothelium is concerned, seems to be retarded.

The mechanism whereby cortisone influences these reactions is in no case clear. However, some features of its activity, such as the delay in the action of the hormone in certain activities (causing decreased capillary permeability or inhibiting fibrous repair, etc.), and particularly the immunity of fibroblasts in tissue-culture (although exposed to a concentration of cortisone 20 times the therapeutic level) in contradistinction to the suppression of their activity in vivo, would seem to indicate the probability of an indirect action through the intervention of an agent or agents unknown, which only become available in the living animal. The fact that intra-ocular activity results from the introduction of a relatively insoluble substance into the conjunctival sac also suggests that the hormone becomes effective through some soluble intermediate product.

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PATHOLOGICAL ACTION OF CORTISONE 707


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