ACUTE INFLAMMATION AND TISSUE MAST CELLS IN ADRENALECTOMIZED RATS WITH CUTANEOUS MUCORMYCOSIS*

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Previous observations have shown that in normal rats the onset of acute inflammation is associated with discharge of the cytoplasmic granules from the tissue mast cells (1-3). In animals with alloxan diabetic acidosis these cells fail to degranulate and the onset as well as the effectiveness of the inflammatory reaction is delayed and impaired (1). Other hormonal abnormalities have also been found to affect the tissue mast cells. Thyroidectomy, as well as administration of iodine and thiourea, alter the dermal mast cell population in rats (4). An excess of either endogenous or exogenous adrenal steroids produces degranulation of the tissue mast cells in man and in several animal species (5-7). Adrenalectomy (8) and hypophysectomy (9) increase their number in various organs of rats. The latter observations relate to tissue mast cells in tissues without inflammation and suggest that the function of these cells in relation to inflammation may be influenced by hormonal factors, a question which does not appear to have been investigated. It becomes also apparent upon review of the literature that the effects of adrenal deficiency on the inflammatory response have not been studied although the results of administration of corticosteroids on the various aspects of inflammation as well as of infection have been extensively investigated (10-13). Several studies in hosts without adrenal tissue have demonstrated the serious consequences of infection associated with the metabolic abnormality (14-17) but have not examined the effects of the altered metabolic state on the inflammatory response.

To test this point, experiments were designed to observe in adrenalectomized rats the histologic sequences of inflammation and the behavior of the tissue mast cells at the site of cutaneous Rhizopus oryzae infection. This fungus was employed since it is not pathogenic in the normal host (1).

Materials and Methods

White male Sprague-Dawley rats, ranging in weight from 180 to 250 gm were used. Adrenalectomized and intact rats were obtained from the Charles River Breeding Laboratories,
ACUTE INFLAMMATION AND TISSUE MAST CELLS

Brookline, Massachusetts. The adrenalectomized animals were maintained on normal saline and standard laboratory chow and were used for experiments on the 7th postoperative day.

All animals were lightly anesthetized with ether and were inoculated intradermally in two sites of the shaved back with 0.2 ml of a standardized spore suspension of *Rhizopus oryzae* (containing approximately 3.5 \times 10^6 spores per ml) to which 1 per cent of sterile India ink had been added to facilitate the identification of the inoculum in the tissues.

After inoculation the 29 intact and the 19 adrenalectomized rats were arbitrarily divided into six groups respectively. One group each was sacrificed by bleeding under ether anesthesia at 30 minutes and 2, 6, 12, 24, and 48 hours after inoculation. No blood pressure determinations were made in either group. Additional controls consisted of 9 normal and 4 adrenalectomized rats which were not inoculated but were otherwise treated in a similar manner.

At the time of sacrifice heart blood was obtained from each animal. The plasma was stored at \(-20^\circ\text{C}\) for several weeks prior to the determination of plasma corticosterone concentrations\(^1\) by the method of Silber et al. (18).

The lesions with the underlying soft tissues, including a wide margin of uninvolved skin, were excised. Complete autopsies excluding the central nervous system were performed; and representative slices of heart, lungs, spleen, pancreas, liver, kidneys, small intestine with attached mesentery, and adrenals, when present, were fixed in Helly's fluid. The histologic preparations were stained with Giemsa.

Earlier studies had shown these methods of sacrifice, fixation, and staining to be effective for the studies of the distribution, number, and appearance of the tissue mast cells (1).

The histologic findings were arbitrarily graded from 0 to 4 plus for the following features: congestion and edema, cellular response, decreased granularity of the tissue mast cells as compared with those of normal uninjured subcutaneous tissue, and the degree of fungal proliferation. The evaluation of the cellular response included margination and diapedesis of neutrophiles, infiltration of tissues by neutrophiles, eosinophiles, and mononuclear cells, clustering of these cells around the fungus and carbon particles (which was regarded as phagocytosis), and proliferation of fibroblasts.

RESULTS

**Biochemical.**—The plasma corticosterone concentrations of the intact rats ranged from 5.0 to 40.0 micrograms per cent (mean 15.4; SEM 1.77). The range in the adrenalectomized animals was from 1.8 to 6.8 micrograms per cent (mean 3.4; SEM 0.299.)

**Morphological.**—Gross examination of the lesions and other tissues showed no significant findings in either group. No residual adrenal tissue was present in the adrenalectomized animals.

**Normal Rats.**—The histologic findings are summarized in Table I. At 30 minutes the skin at the site of inoculation showed marked congestion and edema. Definite margination and some diapedesis of neutrophiles in dilated small blood vessels and early exudation of these cells into the surrounding tissues were present (Fig. 1). At 2 hours neutrophilic margination and diapedesis were already subsiding while exudation into the tissues was marked with beginning clustering of these cells around fungus spores and carbon particles. At the periphery of the lesion some scattered mononuclear cells had appeared and rare fibroblasts

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\(^1\) We are indebted to Dr. Buford L. Nichols, Jr., and to Dr. Claude J. Migeon for the plasma corticosterone determinations.
with prominent nuclei and ample cytoplasm were found. At 6 hours tissue infiltration had reached its peak with many neutrophiles and some eosinophiles surrounding and infiltrating the inoculum thus forming distinct abscesses while leukocytic margination and diapedesis were of minimal degree and extent. The latter were no longer encountered at 12 hours when abscess formation had become more distinct. The cells of the abscesses were beginning to show nuclear clumping. At 24 hours the granulocytes were virtually confined to the abscesses around which fibroblasts and capillaries showed active proliferation. There was also an increased diffuse infiltration by mononuclear cells. Eosinophiles were no longer found. At 48 hours the abscesses were well defined with further increase of mononuclear cell infiltration and fibroblastic activity (Fig. 2).

### TABLE I

**Normal Rats**

<table>
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<tr>
<th>Time</th>
<th>Rat No.</th>
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<th>Tissue mast cells</th>
<th>Fibroblasts</th>
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At 30 minutes the tissue mast cells at the inoculation site showed a marked loss of granules. Free basophilic granules were present in the tissue immediately surrounding the mast cells (Fig. 3). Degranulation was less marked at the periphery of the lesions where an intermediate zone of fully granulated and partially degranulated mast cells was seen. Normal mast cells were present at some distance from the site of injury. At 2 hours no free granules were present in the tissues, and the mast cells near the injection site contained more cytoplasmic granules than at the previous interval. The regranulation was increasingly marked at 6 and at 12 hours (Fig. 4). At 24 hours regranulation was almost complete, and at 48 hours all mast cells were normal in appearance. Tissue mast cells were not identified at any time within the abscesses.

At 2 and 6 hours a few active and rare budding spores were encountered in the lesions but no further proliferation of the fungus occurred. The agent was always confined to the inoculation site and there was no invasion of adjacent tissues or of blood vessels.

Congestion and edema were marked at 30 minutes and decreased thereafter. By 12 hours no congestion and after 24 hours no edema were present.

### Adrenalectomized Rats

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in the exudate. At 2 hours margination and diapedesis of neutrophiles had reached their peak and some clustering of neutrophiles and eosinophiles about the inoculum was present. Mononuclear cell infiltration and fibroblastic proliferation were not seen at this time. At 6 hours margination and diapedesis were still pronounced (Fig. 5) with considerable diffuse exudation into the tissues and early abscess formation. Eosinophiles were less prominent. Mononuclear cell infiltration as well as fibroblastic and capillary proliferation was present. At 12 hours margination and diapedesis of neutrophiles persisted (Fig. 6) and did not disappear until 24 hours. At that time well circumscribed abscesses were present although there was still diffuse infiltration of adjoining tissues with neutrophiles. At 48 hours this infiltration had diminished somewhat but was still prominent (Fig. 7). The abscesses were surrounded by mononuclear cells and granulation tissue with appreciable deposition of collagen.

Degranulation of the tissue mast cells around the site of inoculation was marked at 30 minutes and continued spreading peripherally through the 6th hour (Fig. 8). Evidence of regranulation was first noted at 12 hours and was not complete in some of the rats at 48 hours.

At 6 and at 12 hours the lesions contained some active and rare budding spores. The proliferation of the agent did not progress or involve adjacent tissues.

Congestion of vessels and edema near the inoculation site were present through 24 hours and edema had persisted in some of the animals at 48 hours.

The tissue mast cells in the skin and other tissues of the uninfected normal and adrenalectomized rats were similar in number and appearance.

**DISCUSSION**

The results of the biochemical determinations indicate that no functioning adrenal cortical tissue remained in the adrenalectomized rats while the normal animals produced adrenal cortical hormones. In the normal animals in which the degree of stress was not controlled, the range of plasma corticosterone is from 5.0 to 40.0 micrograms per cent. These values agree with those obtained by others (19) showing a range from 9.0 to 15.0 micrograms per cent with stress capable of causing a thirtyfold increase. In the adrenalectomized rats the values range from 1.8 to 6.8 micrograms per cent and correspond to those of other observers with a range from 3.5 to 6.5 micrograms per cent. These values represent background readings inherent in the method and do not reflect the presence of corticosterone in the plasma of adrenalectomized animals (19). No attempt was made to correlate the corticosterone levels with the various phases of the inflammatory lesions since such correlation is without value except under careful control of the external environment (20, 21) which had not been possible with our facilities.

The findings indicate that morphologic differences exist in the inflammatory reaction of normal and adrenalectomized rats.

In normal animals the exudative cellular processes of inflammation appear early and subside quite rapidly. Granulocytic margination and diapedesis are most marked at 30 minutes, and tissue infiltration reaches its peak at 6 hours. Eosinophiles are not numerous and have disappeared at 12 hours. Circumscription of the inoculum by granulocytes leads to the formation of abscesses which are distinct at 6 hours and become increasingly well defined at 12 and
24 hours. The proliferative cellular processes consisting of mononuclear cell proliferation and granulation tissue formation are first noted at 2 hours and are marked at 24 and 48 hours. At 24 hours the tissues around the abscesses are virtually devoid of granulocytes; and after that time mononuclear cells, fibroblasts, and capillaries account for the increased cellularity of the tissues at the site of injury. The tissue mast cells at the site of inoculation show marked degranulation at 30 minutes and beginning regranulation at 2 hours. They are of normal morphologic appearance at 12 and 24 hours.

In the adrenalectomized rat the exudative cellular processes also appear early but, in contrast with normal controls, reach their peak somewhat later and persist for a much longer period. Granulocytic margination and diapedesis appear at 30 minutes, become most prominent at 2 hours, and continue marked until 6 hours. They decrease thereafter but are still visible at 12 hours and have disappeared only at 24 hours. Neutrophilic infiltration of tissues is most pronounced at 6 hours and persists until 48 hours, decreasing slightly between 6 and 24 hours. Eosinophiles are present in somewhat larger numbers than in the normal rat and some remain in the inflamed area throughout the experiment. Abscess formation is somewhat attenuated, but at 6 hours distinct abscesses are present. They are of the same extent in both groups but somewhat less sharply defined in the adrenalectomized rat, in which the proliferative cellular reactions do not appear until 6 hours. At 24 to 48 hours the lesions resemble those of normal animals, but show some increased collagen deposition at the periphery. In addition, even at 24 and 48 hours, the newly formed granulation tissue around the abscesses contains an admixture of granulocytes as well as mononuclear cells. The tissue mast cells around the inoculum also show degranulation at 30 minutes, but reappearance of the cytoplasmic granules does not occur until 12 hours and in some animals their usual morphologic appearance is not attained completely even at 48 hours.

The behavior of the fungus in the lesions of both groups is similar. The agent remains confined to the site of inoculation and shows no significant proliferation.

In the present experiments the adrenalectomized animals were devoid of both adrenal cortical and medullary tissues. The adrenal medullary hormones do not appear to affect the inflammatory response directly by the action of epinephrine (22) or indirectly through the induction of hypotension. Persistent lowering of the blood pressure does not follow adrenalectomy in rats (23).

It appears that in the absence of the adrenal the onset of the acute inflammatory response of the rat is slightly attenuated and that the duration of the exudative granulocytic reaction is distinctly protracted.

Results in keeping with the above findings have been reported by Delaunay and co-workers (22, 24) who found a somewhat increased tissue neutrophile response to toxic...
doses of typhoid vaccine in adrenalectomized rats when compared with intact animals. Speirs and his associates (25) have observed a greater concentration of neutrophiles in adrenalectomized than in normal mice at 4 and 12 hours after intraperitoneal injection of antigen. Fruhman (26) has failed to encounter changes in peritoneal fluid neutrophilia in adrenalectomized as compared with intact rats but the observations were made only at a single time interval 5 hours after injection of an irritant.

Previous observations have suggested that degranulation of tissue mast cells at the site of injury with the release of substances associated with the granules such as histamine and 5-hydroxytryptamine may be a factor in the initiation of the acute inflammatory response (1–3, 27). The present findings also show a correlation between degranulation of tissue mast cells and granulocytic exudation. In the normal rat degranulation and reappearance of granules in these cells respectively coincide with the onset and subsidence of granulocytic exudation. In the adrenalectomized animal a similar correlation is found although degranulation of tissue mast cells and granulocytic exudation, while first appearing at the same time as in the normal rat, persist for a much longer period. It appears therefore that in the rat the absence of the adrenal glands affects the function of the tissue mast cells in their relationship to the inflammatory response.

The known suppressive effect of the adrenal cortical hormones on eosinophiles (28) is reflected in the earlier appearance, greater numbers, and protracted presence of these cells in the lesions of the adrenalectomized animals. Studies on the peritoneal tissue mast cells in rats have suggested that the eosinophiles inactivate the products of these cells by phagocytosis of discharged granules (29). In the present study only occasional neutrophiles and rare eosinophiles show such phagocytosis and there is no difference between the two groups of animals. Therefore the relative eosinophilia in the lesions of the adrenalectomized rats does not appear to account for the differences in the inflammatory response.

The absence of the adrenal might also account for some of the differences in the proliferative inflammatory responses of the two groups of rats. The first signs of fibroblastic activity occur in the intact animals at 2 hours but are not noted until 6 hours in the adrenalectomized host. Despite the initial delay fibrosis is more marked in the latter toward the end of the experiment. The increased fibrosis may well be related to the absence of adrenal cortical hormones which are known to inhibit fibrosis tissue formation (30), although Riley has suggested that the products of the tissue mast cells stimulate the fixed connective tissue elements. Prolonged mast cell degranulation may thus induce increased fibrosis (31). The delayed onset of fibroblastic activity in the adrenalectomized rat may be connected with altered tissue mast cell function and with the retardation of the mononuclear cell response. These cells, which by some (32, 33) are thought to form fibroblasts, appear first at 6 hours in the adrenalectomized animal in contrast to the intact rat, in which they are already discernible at 2 hours. The relationship of adrenal deficiency to the mononuclear cell phase of inflammation is not clear at present. It is possible that the differences in the inflammatory response of two groups are related to differences in the biochemical composition of the inflammatory lesions. Adamkiewicz (34) has shown that the exudate in croton oil-induced granuloma pouches of adrenalectomized rats contains significantly more total reducing sugar, fats, and potassium than comparable lesions in normal animals. Concentrations
of total protein, non-protein nitrogen, and chlorides, as well as pH and volume of exudate did not differ in the two groups.

Our results indicate that in rats the absence of the adrenal does not enhance cutaneous \textit{Rhizopus oryzae} infection although it affects the regulation and alters the course of inflammation. Similar observations have been reported by others who have noted that the lesions of experimental trypanosomiasis (16) and bartonellosis (17) in adrenalectomized rats did not differ from those of normal animals although the mortality of the animals without adrenals was greatly increased. The lack of fungus proliferation in the lesions of adrenalectomized rats in the present study probably reflects to some extent the low natural pathogenicity of the fungus which is advantageous since it avoids the toxic systemic effects associated with many other infections. These effects impose additional demands on the biochemical state of the host with adrenal deficiency and account for the clinical and experimental observations that in patients and animals with untreated Addison's disease even minor infection may produce serious consequences (35). The course of the fungus infection in the adrenalectomized rats is entirely different from that of animals with acute alloxan diabetes and acidosis in which the abnormality of host metabolism impairs inflammation and invariably induces growth of the fungus with spread of the infection (1). These experimental data closely correlate with the clinical observation that patients with untreated diabetes mellitus and acidosis are greatly susceptible to infection. The lack of fungus growth in the lesions of adrenalectomized rats suggests that the abnormal metabolic state of adrenal deficiency alters but does not primarily impair the effectiveness of the inflammatory response and correlates with the absence of documented evidence that the incidence of infections in patients with untreated Addison's disease is increased.

**SUMMARY**

The effects of the absence of adrenal tissues on the inflammatory reaction and on the relationship of the tissue mast cells to the inflammatory process have been studied histologically in rats with cutaneous \textit{Rhizopus oryzae} infection. Degranulation and regranulation of the tissue mast cells at the site of injury have been found to correlate respectively with the onset and subsidence of the exudative cellular phase of inflammation. In the adrenalectomized animals regranulation of these cells and correspondingly termination of the exudative phase are delayed. In the lesions of these rats the numbers of eosinophiles are increased. The proliferative cellular processes of inflammation, although delayed in onset, progress in essentially normal manner but result in some increased collagen deposition. The lack of adrenal secretions does not enhance fungus proliferation and is not associated with spread of the in-
fection. In the present experiments the effectiveness of inflammation does not differ in normal and adrenalectomized rats.

The technical assistance of Miss Hillma Gheesling is gratefully acknowledged.

BIBLIOGRAPHY


17. Marmorston-Gottesman, J., and Perlis, D., The effect of bilateral suprarenalec-


EXPLANATION OF PLATES

PLATE 6

**FIG. 1.** Normal rat, 30 minutes. Congested venule with granulocytic margination, diapedesis, and early tissue infiltration. Giemsa. × 500.

**FIG. 2.** Normal, 48 hours. Note virtual absence of cellular infiltration in tissues surrounding abscess. Giemsa. × 300.
(Paplanus and Sheldon: Acute inflammation and tissue mast cells)
Fig. 3. Normal, 30 minutes. Discharge of cytoplasmic granules from three mast cells (arrows). Giemsa. X 750.

Fig. 4. Normal, 6 hours. Regranulation of tissue mast cells (arrows). Giemsa. X 750.
(Paplanus and Sheldon: Acute inflammation and tissue mast cells)
PLATE 8

Fig. 5. Adrenalectomized, 6 hours. Congested venule with granulocytic margination and diapedesis. Giemsa. × 500.

Fig. 6. Adrenalectomized, 12 hours. Diffuse, chiefly granulocytic, tissue infiltration, and congested venule (arrow) with slight persistent granulocytic margination and diapedesis. Giemsa. × 500.
(Paplanus and Sheldon: Acute inflammation and tissue mast cells)
PLATE 9

FIG. 7. Adrenalectomized, 48 hours. Compare with Fig. 2 and note diffuse cellular infiltration of tissues surrounding abscess. Giemsa. × 300.

FIG. 8. Adrenalectomized, 2 hours. Discharge of cytoplasmic granules from three tissue mast cells (arrows). Phagocytosis of granules by neutrophiles (lower right). Giemsa. × 1000.
(Paplanus and Sheldon: Acute inflammation and tissue mast cells)