

THE EBB AND FLOOD OF THE EOSINOPHILS IN THE BURNED PATIENT AND THEIR USE IN THE CLINICAL MANAGEMENT*

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INTRODUCTION

"There is a tide in the affairs of men,
Which, taken at the flood, leads on to fortune;
Omitted, all the voyage of their life
Is bound in shallows and in miseries."

*William Shakespeare,
Act IV, Scene III, Julius Caesar.*

IN RECENT SURGICAL LITERATURE, attention has been called repeatedly to the drop in circulating eosinophil cells which occurs immediately following operations and other types of surgical stress.^{1-4, 8} The number of burned patients studied has been limited, however, and insufficient attention has been paid to the resurgence of the eosinophils during the weeks and months of infection, wound healing and convalescence. It is common knowledge that the eosinophil count may rise to high levels in Addison's disease, allergic reactions, myelogenous leukemia, Hodgkin's disease and in parasitic infestations, to name only a few conditions with which eosinophilia may be associated. To these we would like to add the later phase of infection, wound healing and convalescence from extensive burns.

PATIENTS AND METHODS

This report is based upon studies made in 31 burned patients admitted to the Massachusetts General Hospital since 1950. Twenty-two were admitted the day of injury and studied from the outset. Five patients were not transferred to this hospital

until several days or weeks postburn. They were followed from the time of admission. In the other four cases, although admission was prompt, eosinophil counting was deferred. Two were placed under study within 72 hours, one within 12 days and the last not until the 54th day following the burn. The extent of the burns ranged from 2 to 68 per cent of the body surface; from zero to 30 per cent being of third degree. Two-thirds of the patients were males. The ages ranged from two to 87 years. Ten patients, four of them women and six men, failed to survive.

Treatment consisted of routine measures in the majority of cases. In three of the patients ACTH or cortisone was administered as a part of a study of the effect of the hormones on the increased capillary permeability of burns, and on the survival of homografts. The results of those studies are reported elsewhere.^{6, 10} One of the patients, an 81-year-old white woman who sustained burns of 20 per cent of her body surface while rescuing a blind woman from a flaming room, was given 100 mg. of ACTH daily in divided doses for five days, followed by gradual reduction of the dosage to 80, then 60, and finally 45 mg. per day. The duration of the course was 54 days (Case 50-26).

A second patient treated with ACTH was an 18-year-old boy with third degree burns of both lower extremities. He had received 1,550 mg. over an eight-week pe-

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riod prior to admission to the Massachusetts General Hospital. The daily dose is reported to have been between 60 and 80 mg. for the first ten days and never less than 10, nor more than 20 mg. thereafter (Case 50-20). A second course of treatment with ACTH was given in the seventeenth month after his injury, because of a persistent dermatitis of his grafted legs which failed to respond to bed rest and the customary dermatologic measures. One hundred mg. were given daily for two days, and then the dose was slowly reduced to 25 mg. daily. After 11 days, intravenous administration was substituted for the intramuscular route and the dose increased to 50 mg. The course of therapy was terminated after 22 days.

The single cortisone-treated patient to be described was a 45-year-old man who tripped and fell, plunging both hands to the wrists in hot asphalt. He was treated with cortisone for the first 20 days. For 18 days, he received 100 mg. daily; on the last two days 50 mg. and 25 mg. respectively. The drug was administered intramuscularly for the first eight days, and orally thereafter.

Eosinophil counts were carried out at intervals during the patients' hospital course. Venous rather than capillary blood samples were used. An effort was made in each case to withdraw blood for study during the same period of the day. This precaution seemed advisable in view of the regular morning fall and afternoon rise in circulating eosinophils noted by others^{5, 9} and confirmed by our own observations on normal subjects.

The blood for the eosinophil counts was mixed gently with Ham's oxalate solution, carried to the laboratory and diluted promptly in the phloxin-propylene glycol solution recommended by Randolph.⁷ Only white cell diluting pipettes certified by the National Bureau of Standards were used. Dilutions varied from 1:10 for low counts to 1:33 $\frac{1}{3}$ for the highest counts. Counting

was done in Fuchs-Rosenthal counting chambers, both sides of two chambers being counted. A minimum of 23 minutes and a maximum of four hours elapsed between dilution and counting, the overwhelming majority of the counts being made within an hour of dilution.

RESULTS

THE INITIAL DROP IN CIRCULATING EOSINOPHILS WAS SEEN IN ALL BUT THE MOST MINOR BURNS

In 21 out of 22 patients in whom eosinophils were counted during the initial 12 hours post-burn, the number was below normal (Fig. 1). In the four patients in whom two or more counts were made in the first hours, a falling level was recorded (Fig. 2). The level to which the count descended was not related to the extent of burn except in the burns of least extent. Counts below 5 per cu.mm. were noted both in patients with burns involving 6 to 10 per cent of their body surfaces, and in those with burns of 20 to 68 per cent. In six patients with burns of less than 5 per cent, however, the initial level was not as depressed as in the more extensively burned cases. There were no counts below 25. In one, the level was never below normal, although a slight drop occurred between the first two counts. In two, slight drops were demonstrated, but the drops were within the limits of error of the counting method.

THE CUSTOMARY REAPPEARANCE OF CIRCULATING EOSINOPHILS DURING THE EARLY DAYS POST-BURN

In all patients surviving their burns, the eosinophil cells began to reappear at least by the third day, and in many cases by the first day post-burn. The rate of rise varied considerably from patient to patient. The data in Figures 2 and 3 suggests that the rate of rise is slower in patients with severe burns than in those with burns of lesser extent. Patients with 10 or 15 per cent burns have shown counts in the four hundreds as early as their sec-

ond week post-burn, whereas in patients with burns of 20 to 30 per cent, equally high counts are not noted until the sixth or seventh week. Figure 4, on the other hand, shows similar eosinophil changes

THE FLOOD TIDE OF CIRCULATING EOSINOPHILS IN THE LATER DAYS FOLLOWING SEVERE BURNS
In severely burned patients who survive, there is a gradual flood tide of eosinophils which in later weeks may reach

TABLE I.

Case Number	Percent Burn	Percent Third Degree	Time of Eosinophil Counts and Rise	Peak Count	Time Peak Count Reached	Subsequent Changes in Eosinophil Counts	Clinical Course
49-1	35%	10%	Count reached 810 by 8th week	2,126	18th week	Count was still above 1,000 on discharge in 20th week. It had dropped to 68 on re-visit at 6 mo.	Sluggish, but never critically ill
50-2	30%	15%	Count reached 218 by 4th week	544	6th week	Count returned to 140 by 9th week	Stubborn infection in one wound but course satisfactory
50-10	21%	20%	(No counts were made between 3rd and 7th weeks)	731	7th week	Count fell to 235 by 9th week	Satisfactory
51-43	68%	30%	Count reached 550 by 5th week.	804	9th week	Count still at 395 on discharge 23 weeks post-burn	Satisfactory

TABLE II.

Patient	% Burns	% 3°	Days Post Burn	Eosinophil Count pre-ACTH (± twice the standard error)	Eosinophil Count 4 hours post-ACTH 25 mg.	% Drop
#50-10	21	20	48	701 ± 66	378	46%
#51-43	68	30	85	509 ± 57	370	27%
#50-20	40	32	77	112 ± 27	92	(Not significant)

occurring in two patients with burns of quite different extent and severity. Here again there is no consistent correlation between extent of the burn and eosinophil level. Reasons for this will be apparent below when the effects of infection, dressings, anaesthesia and operations are considered. Each of these tends to maintain an eosinopenia. The virulence of infection and the number and sequence of operations varies widely in patients with burns of comparable extent.*

previously unrecorded levels. Six patients in the series survived burns of 20 per cent to 68 per cent. Of these, four can be discussed together. They received no hormone therapy and ran relatively uncomplicated courses. These patients exhibited a gradual rise in eosinophils to unexpectedly high levels in the later weeks of illness. Abnormally high counts ranging from 400 to 2,000 were encountered during the second, third and fourth months after injury. The duration of the eosinophilia varied from

* Evans and Butterfield have found a significant correlation between extent of burn and the average of the eosinophil counts for the first ten days.⁵ Perhaps their program of dressings and operations for the first ten days is more standard-

ized than is ours. Our program is irregular, tailored to what we consider are the patient's needs and, therefore, not infrequently includes surgical excision and grafting within the first week after injury.

one week to several months (Fig. 3 and Table I). The clinical state of the patients was progressing satisfactorily throughout the period of their eosinophilia. A less marked eosinophilia was noted in four of the patients with smaller, less severe burns (Fig. 2).

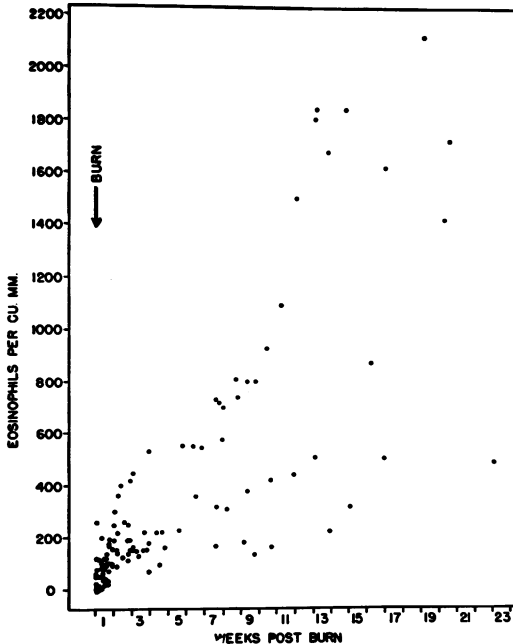


FIG. 1.—The pattern of initial low eosinophil count and subsequent gradual rise in eighteen burned patients surviving their burns. Counts of the three surviving patients who received hormone therapy are not shown.

THE OMINOUS SIGNIFICANCE OF PERSISTENT OR RECURRING EOSINOPHENIA

Failure of the Eosinophils to Reappear After the Initial Drop. Eight of the 29 patients failed to show the expected rise in eosinophil count during the early days post-burn. The counts remained below 33 and all died between the first and the fifteenth day. The counts of these eight are depicted in Figure 5, together with case 50-23 described in the next section.

Secondary Falls in Circulating Eosinophils. Secondary falls in eosinophil counts were frequently observed. They occurred quite regularly following burn dressings, skin grafting procedures or the development of complications (Case 50-2, Fig. 4).

In one patient, a drop in the circulating eosinophil level heralded the coming of renal failure and death (Case 50-23, Fig. 5). A similar secondary fall was noted in another patient who developed severe sepsis during the sixth week post-burn; he became comatose and was critically ill. With

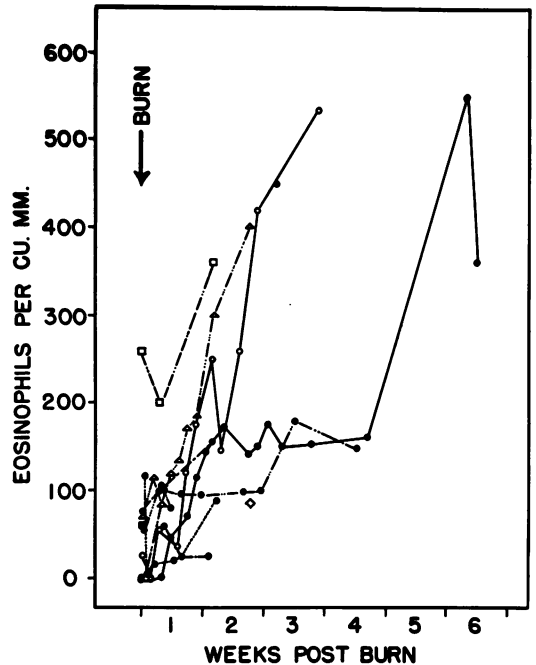


FIG. 2.—The pattern of eosinophil cell reappearance in thirteen patients with burns of less than 20 per cent of their surface areas.

changes in chemotherapy, he improved temporarily and his eosinophil count rose, but only to 168. Later, with extending sepsis including thrombophlebitis, abscess formation and terminal pneumonia, his counts were reduced to less than 15. His counts are not charted.

Failure of the Eosinophils to Soar in the Second to Fourth Month. In the period from the second to the fourth month after injury when the four patients with relatively smooth courses showed eosinophilia, two of the extensively burned patients failed to show the flood tide of eosinophils. Both were critically ill; one died in the fifteenth week post-burn, never having had an eosinophil count above the normal value

of 167. He was a 57-year-old man who had been deeply burned over 23 per cent of his body surface by furnace flames and ignited clothing. A thin man, he proved a feeding problem. He reacted irregularly to operative procedures. His wounds were badly infected, and he was intermittently comatose. He developed septic thrombo-

and finally glomerulonephritis brought the patient near to death. In his twenty-fourth week, he had a convulsion and was comatose for several days. All circulating eosinophils had disappeared. With gradual improvement, the eosinophils reappeared and the count rose. He was discharged after seven months, apparently an exception to the rule of developing eosinophilia with improving general condition. On readmission because of his dermatitis in the seventeenth month post-burn, however, his eosinophils were found to number 1,462 per cu.mm. He was given his second course of ACTH on that admission, and some improvement was noted in the dermatitis. His eosinophilia decreased, but was not completely suppressed by the hormonal therapy. On the eighth day of ACTH treatment, his circulating eosinophils had fallen to 1,073 cu. mm. and on the eleventh to 500. The count remained fairly constant at that level for a week thereafter, then rose to 800 while the patient was still on ACTH. It finally surged to 1,616 three days after ACTH was discontinued.

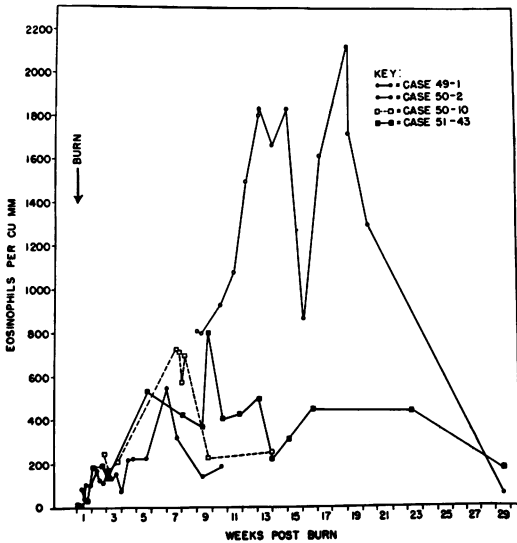


FIG. 3

FIG. 3.—The soaring of eosinophil counts late in the course of four patients with burns of from 20 to 68 per cent of their surface area. Clinical progress of all was satisfactory.

phlebitis in both legs and one arm, with a staphylococcal abscess and terminal septicemia. His counts are not charted.

The second patient was the 18-year-old boy with full thickness loss of the skin of both legs and thighs, who had received ACTH for eight weeks prior to admission to this hospital. Despite the alleged appetite-stimulating effect of ACTH, he had arrived at this hospital in an advanced state of malnutrition. His eosinophil count on admission was 268 cells per cu.mm. and it remained below that level through his seventh month after injury (Fig. 6). This boy's course was also stormy, and his counts remained low. Sepsis, repeated dressings, skin grafting procedures requiring anesthesia,

In two other patients, the flood tide of eosinophils failed to appear at the expected time, but they received hormone therapy. Their courses are described in the following section.

EFFECT OF ACTH OR CORTISONE ON CIRCULATING EOSINOPHILS

Early ACTH or Cortisone Therapy Postpones the Reappearance of Circulating Eosinophils After the Initial Fall. Hormone therapy delays the reappearance of the eosinophils. In the heroic 81-year-old lady who received ACTH for the first 54 days, the eosinophil count remained below 70 for the first 20 days, then rose gradually to 380 despite continued therapy. When hormonal treatment was discontinued, the number of circulating eosinophils shot upward (Fig. 7). The patient's clinical course was excellent throughout her hospital stay despite her age and the extent of her burns (20 per cent, 7 per cent of third degree).

The eosinophil count of the man treated with cortisone for 20 days post-burn also remained low longer than anticipated. His burns were of mixed second and third degree of both hands, involving approximately 4 per cent of his total body area ($\frac{1}{2}$ per cent of third degree). In other patients with burns of such limited extent, a

hospital course. Because of the diurnal variations in the number of circulating eosinophils, the tests were carried out in the afternoon. A drop in count following ACTH is less subject to misinterpretation if it is observed at the time of an expected rise, rather than during the period when the eosinophils are usually decreasing in num-

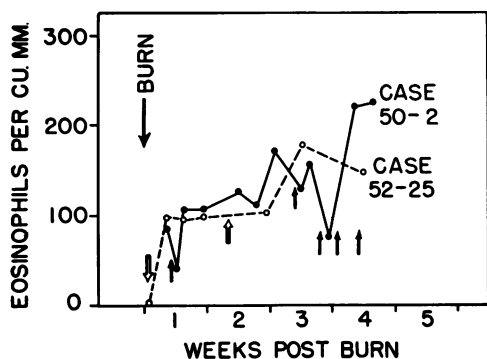


FIG. 4

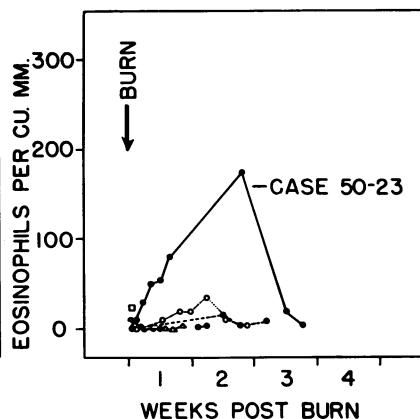


FIG. 5

FIG. 3.—The soaring of eosinophil counts late in the course of four patients with burns of from 20 to 68 per cent of their surface area. Clinical progress of all was satisfactory.

FIG. 4.—The course of the eosinophil counts in two patients with burns of different extent and severity. Case 50-2 sustained burns of 30 per cent of his surface area, half of which was of full thickness requiring grafting. Case 52-25 had burns of only 6 per cent, one third of which required grafting. The five solid arrows indicate dressing changes and debridement under anesthesia in the more severely burned patient, showing the manner in which operative procedures may influence the eosinophil level. The first three procedures were followed by a drop in the eosinophil count. (The subsequent course of his eosinophils is given in Figure 3.) The two open arrows indicate the grafting operations in the less severely burned patient. No fall in eosinophil count was recorded following the second procedure. The count was already at zero before the first.

FIG. 5.—The course of the eosinophil count in nine patients who succumbed. In eight patients the eosinophils failed to reappear after the initial drop. There was no count above 33. Such continued eosinopenia is considered ominous. The ninth patient, Case 50-23, exhibited a transient rise and subsequently, with development of renal failure, showed a fall before death.

prompt reappearance of eosinophils within 48 hours was observed. In this cortisone-treated patient, the counts were below 50 for the first five days. They rose slowly thereafter, reaching 149 on the sixteenth day of therapy. Four days after cortisone was stopped, the count had risen to 203 (Fig. 8). The patient was then discharged from the hospital and could not be followed further.

ACTH Administered in the Later Weeks Post-burn Reduces Eosinophilia if Present. Isolated ACTH tests (25 mg. I.M.) were performed on three patients late in their

ber. A smaller percentage drop is to be expected from ACTH tests performed in the afternoon than from morning tests. Two of the patients had high counts when the ACTH was administered, and both showed good responses (Table II).

The third patient (Case 50-20), the 18-year-old boy whose life hung precariously in the balance for months, had a count of only 112 at the time the test was performed two and one-half months post-burn. Four hours after ACTH administration, there were still 92 eosinophils per cu.mm. The drop is not statistically significant.

injury indicates that the patient is tolerating his burden and may bear up well under additional surgical procedures.

An eosinophilia may, of course, presage adrenal failure. We do not think we have encountered adrenal insufficiency in our patients, because the patients have all been improving during the flood tide. The possibility of adrenal failure must be kept in mind, however, and the finding of an

nor entirely ruled out. Antibiotic therapy does not appear to be a determining factor. The four patients in our series exhibiting the high tide of the eosinophils were on penicillin, but three showed a subsequent decline while still on the drug. The duration of administration of other antibiotics was too short to bring them under suspicion as allergens. The possibility of bacterial allergies has not been investigated.

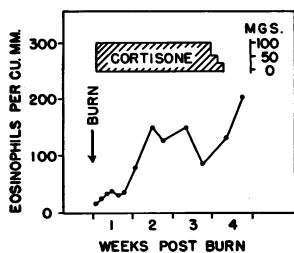


FIG. 8

FIG. 8.—The course of the eosinophils in a patient treated with cortisone. The burns were circumscribed, involving both hands only. In other patients with similar burns not treated with cortisone the eosinophil count rose promptly during the first week. In this case the eosinopenia was prolonged. In spite of the cortisone the eosinophil count was at normal levels during the second and third weeks. The patient was treated with cortisone for the first 20 days. The drug was administered intramuscularly for the first eight days and orally thereafter.

FIG. 9.—White counts of the four patients with burns of 20 to 68 per cent of their body surface who received no hormone therapy. Compare with Figure 3. There is no consistent correlation between eosinophil and total leucocyte counts. Leucocytosis may accompany the initial eosinophil drop. Normal counts are seen at the time of the late eosinophilia of severe burns.

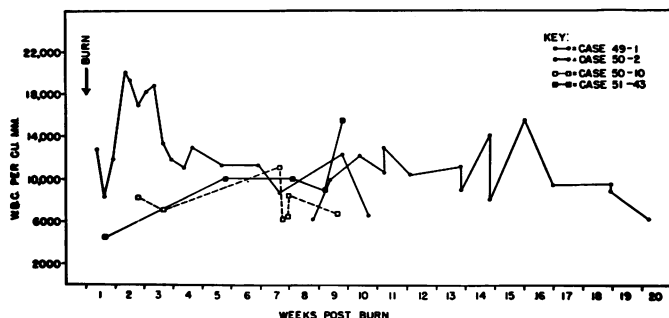


FIG. 9

eosinophil count above 400 in the first week or ten days following an extensive deep burn should make one suspect such failure.

The reason for the high tide of eosinophils is not apparent. There are several possibilities. The eosinophilia may be due to an intensified eosinophil cell production, release of eosinophils from storage, an increased resistance of the cells to destruction, diminution in the forces tending to destroy or store the eosinophils, or any combination of these. Simultaneous measurement of the total leucocyte count negates the theory that the eosinophilia is a part of a general leucocytosis.

In our experience, the hypothesis that allergy plays a role in the development of the eosinophilia has been neither supported

SUMMARY

1. The course of the blood eosinophil count has been observed in 31 burned patients during their hospital stay.

2. A prompt drop in the number of eosinophils in the circulating blood is to be expected immediately following burn trauma. In 21 out of 22 patients in whom eosinophils were counted during the initial 12 hours post-burn, the number was below normal.

3. The level to which the eosinophil count descends does not correlate with the extent of the burn, except in minor injuries. The count in patients with moderate burns may drop maximally, as it does in the extensively burned. There may be little or no eosinopenia in patients with minor burns.

4. In patients showing satisfactory clinical progress, a rising eosinophil count appears by the third post-burn day. The rapidity of the rise is not necessarily related to the extent of the burn, for it may be retarded by infection and operative procedures.

5. Failure of reappearance of eosinophils by the third day post-burn is a grave prognostic sign. Eight out of 29 patients failed to show a rise above 33 eosinophils per cu.m. in the first week. All eight died.

6. Secondary falls in eosinophil count are to be expected following burn dressings and skin grafting operations. Falls are reported after such procedures in seven cases.

7. A secondary fall in eosinophils unexplained by a recent surgical procedure heralded the development of a complication in three patients. In two, it was associated with an aggravation of sepsis and in the third, renal failure with subsequent death; the ninth death in our series. Thus failure of reappearance of eosinophils, or persistence of a low count after operation or a complication, suggests poor tolerance to the existing stress and warns against infliction of an additional major operation.

8. A flood tide of eosinophils, counts ranging from 400 to 2,000, is to be expected during the later weeks or months in extensively burned patients making satisfactory progress. Such an eosinophilia is described in four patients.

9. The absence of the flood tide of eosinophils in the extensively burned patient during the second, third or fourth months post-burn may have grave significance.

10. ACTH or cortisone alter the expected eosinophil pattern. In two patients receiving one or the other hormone, the expected

rise of eosinophils from the initial low levels was postponed, but not prevented.

11. The eosinophil count bears no consistent relation to the total leucocyte count.

12. The possible origins of the high tide of eosinophils in extensively burned patients is discussed.

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The hormones used in these studies were generously supplied, the ACTH by the Armour Laboratories and the Cortisone by Merck & Co.

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