with the small motor system in frogs the contractile effect upon the muscle fibre is the final event, with the small motor system in mammals this is not so. Here the contraction presents an intermediary stage; it acts as a mechanical stimulus for exciting the nerve endings in the spindle and thus sets up an afferent discharge. We shall probably hear much more about this system in the future.

It may be felt that when discussing the small-motor-fibre system I should have confined myself to mammalian muscle. But we are not certain whether the more primitive mechanism of producing sustained contraction in frogs and crustacea may not exist in some mammalian muscle—for instance, in the eye muscle. Further, under abnormal conditions—for instance, after denervation—the mammalian skeletal muscle reverts to the more primitive form of response; that is, localized contracture. This phenomenon is understandable only under the wider phylogenetical aspect. But the main reason is that I found it so fascinating to see how Nature ingeniously adapts parts of an old system, the small-motor-fibre system, to a more complicated mechanism in the development of postural reflexes in higher animals, that I could not resist giving the full story so far as it has been unravelled by recent experiments.

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EOSINOPHIL AND OTHER LEUCOCYTE CHANGES IN BURNED PATIENTS

WITH SPECIAL REFERENCE TO ADRENO- CORTICAL ACTIVITY

BY

S. SEVITT, M.D., F.R.C.P.I., M.Sc., D.P.H.

Pathologist, M.R.C. Burns Research Unit and Birmingham
Accident Hospital

An injection of anterior corticotrophic hormone of the hypophysis (A.C.T.H.) produces a marked fall in the eosinophils in the blood, associated with lymphocytopenia and neutrophil leucocytosis: in patients with Addison's disease, however, cortisone, but not A.C.T.H., produces similar effects (Thorn *et al.*, 1947a; Dougherty and White, 1947; Forsham *et al.*, 1948; Hills *et al.*, 1948; Prunty, 1950). The leucocyte changes, therefore, are mediated through adrenocortical stimulation by the anterior pituitary. Selye (1950) maintains that the major endocrine response to stress is an increased secretion of A.C.T.H. by the pituitary, which induces glyco-corticoid secretion by the adrenal cortex. The cortical hormones act on the peripheral organs and produce eosinopenia, lymphocytopenia, and neutrophilia.

The initial polymorphonuclear leucocytosis in burned patients is well known (Locke, 1902; Dorrance, 1933; McIver, 1933; Brown, 1944), and reference has been made to eosinopenia (Schreiner and Pucsko, 1925; Crassweller *et al.*, 1950a). The purpose of this study was to follow the changes in number of the blood leucocytes of recently burned patients and to correlate the findings with the extent of burning and other factors. In this way it was hoped to gain information on adrenocortical activity.

The Burned Patients

Thirty-five patients (19 males, 16 female) were studied; they were all between the ages of 13 months and 80 years and the extent of burning varied from 0.1% to 80% of the body area (Table I). Twenty-seven were admitted to the Burns Research Unit within three hours of burning, most within an hour or two, and all within nine hours. Twenty-four were or became clinically shocked and 26 were transfused with plasma or dextran or both fluids.

Eight patients died—two were moribund on admission and died a few hours later, five died two to four days

TABLE I.—*The Burned Patients*

Case No.	Sex and Age (Years)	Clinical Shock	Body Area Burned	Sites of Burning	Lived or Died and Day of Death
1	M 18/12	—	0.1%	Left hand	Lived
2	M 33	—	4%	Small metal burns face, neck, right arm, and back	"
3	M 25	—	4%	Both hands and arms	"
4	M 15	—	5%	Face, hand	"
5	M 4	—	7%	Scald right leg	"
6	M 13	+	9%	Back, right arm, shoulder, axilla	"
7	M 35	—	8%	Face, both hands, wrists	"
8	F 2	±	9%	Back	"
9	F 2½	±	7%	Back	"
10	M 13/12	±	10%	Scald left chest, left hand	"
11	M 50	±	11%	Face, chest, arms, thighs	"
12	F 4	±	11%	Right arm, right thigh, chest	"
13	M 23	+	12%	Face, neck, upper chest, hands	"
14	F 4	±	13%	Right upper chest, axilla, face, thighs	"
15	M 2	+	15%	Lower face, chest, upper abdomen, front thighs	"
16	F 55	+	17%	Scalds legs	"
17	F 3	+	18%	Abdomen, back, thighs, left arm, right hand	"
18	F 2	+	20%	Back of chest to buttocks	"
19	F 68	+	22%	Scalds left upper arm, left side of trunk and buttock	"
20	M 28	+	25%	Face, arms, chest, back	"
21	F 2½	+	25%	Scalds back, buttocks, leg, flank, left arm	"
22	M 38	++	26%	Right arm, left forearm, hand, face, scalp, right leg	"
23	M 20	++	30%	Face, neck, chest, arms	Died, 2
24	F 13	+	30%	Half lower back, buttocks, thighs, and inside right forearm	"
25	M 4	+	30%	Chin, neck, chest, abdomen, upper thighs	Lived
26	F 58	++	35%	Abdomen, buttocks, perineum, thighs, left arm	Died, 3
27	F 3	+	36%	Abdomen, buttocks, thighs, arms	Lived
28	M 80	++	40%	Buttocks, lower abdomen, thighs, scrotum, upper legs	Died, 0
29	F 9	++	42%	Face, neck, arms, trunk, thighs	Died, 2
30	F 5½	++	47%	Arms, trunk, thighs	Lived
31	F 8	+	47%	Front chest, abdomen, buttocks, thighs, hands	"
32	M 36	++	50%	Face, trunk, arms, forearms	Died, 9
33	M 27	+	65%	Face, neck, both arms, hands, chest, back, right thigh	Lived
34	F 5	++	75%	Whole trunk, neck, arms, thighs, legs	Died, 2
35	M 22	++	80%	Entire body except feet and lower legs	Died, 0

0 = Day of burning; 1, 2, etc., following days.

Shock: — absent, ± doubtful, ± slight, + definite, ++ severe.

after burning, and the other on the ninth day. Twenty-one patients were discharged with healed or successfully grafted burns 1 to 15 weeks after admission, and at the time of writing the remainder have been in hospital 2 to 12 weeks and are doing well.

A patient with, say, 10% of his body surface burned is referred to as a 10% burn. In certain analyses the patients are grouped into 0–10%, 11–20%, 21–30%, and more than 30% burns.

Outline of Treatment.—At the initial dressing 1% cetrimide was used to clean the skin and then penicillin cream, often supplemented by polymyxin cream, was applied. Local sulphonamides were not used. This was fortunate, as Brown (1944) found that sulphonamide cream depressed the leucocyte count. In the non-shocked patients skin-grafting of deep burns was generally carried out on the first or second day. Shock was combated by intravenous plasma or 6% dextran in saline, or both, and repeated haematocrit observations were made. Sometimes blood transfusions were given. In shocked patients skin excision and grafting was delayed for a week or longer. Blood transfusion was given for anaemia and during most of the operative procedures. Diet was of the high-calorie high-protein type.

Methods

Blood counts were from ear or finger-prick blood, the first drop being discarded. Differential counts were made from Leishman-stained films on slides, and at least 400 leucocytes, often 600 to 1,000, were enumerated. In this paper the neutrophil polymorphs, metamyelocytes, and myelocytes are grouped as neutrophil cells.

Eosinophil counts were carried out by the direct "wet-field" method of Dunger (1910). Every few days the diluting fluid, consisting of 1 ml. of 1% aqueous eosin Y, 1 ml. of acetone, and 18 ml. of distilled water, was freshly prepared, and each day it was filtered. Blood was diluted 1 in 20 with this fluid in each of two white-cell pipettes: within a few minutes a double-sided Fuchs-Rosenthal chamber was filled from each pipette and the eosinophils in four entire fields were counted. The volume of the blood containing these cells was 0.65 c.mm. A number of parallel counts by both Dunger's (1910) and Randolph's (1949) methods gave very close results.

In the first 18 cases the counts were usually performed twice daily during the first three to five days after burning, daily for the next week, and thereafter every two to four days until discharge. The general pattern of leucocyte changes had by then been established. Only eosinophil counts which were regarded as of special interest were carried out on the next 17 patients. They were usually performed four times a day during the period of eosinopenia and at the beginning of the post-eosinopenic rise (see below), twice daily during the next few days, and thereafter less often.

In 16 patients several eosinophil counts were made at about hourly intervals for three to six hours on the day of admission. The first counts were performed on 11 patients within two hours of burning, on 11 others within the third hour, and on all within 24 hours.

TABLE II.—*The Eosinophil Counts per c.mm. of Blood in 19 Patients, Showing the Development of Eosinopenia After Burning*

Case No.	Hours after Burning								
	1–	2–	3–	4–	5–	6–	7–	8–9	18–30
1		68	40	28	19				9, 31
5	1,270		276	87					42, 192
7	177	100	26	18	9	21			47, 90
9		716	767	450	165			99	31, 87
11		50	19						0, 0, 0, 0
12		53	11	5		0			0, 3, 2, 7
14		304		32		6			0, 0
15	6						0		3
16	74	31	25	3	0				0, 0
17			29	8	0				0, 6, 4, 4
18					11	5	0		0, 0, 0
20	20		0						0, 0, 0
21	281	212	56					6	0, 3
25	13								0, 3
26	19	14	3	0					0, 0, 0, 0
28	257	276	268*						
32		19	34		0				0, 0
33	170		36	11		9	0		20, 3, 8, 11
35		174	71	55	*				

* = Time of death.

Normal Eosinophil Values.—In our experience the eosinophil level in normal subjects usually varies between 100 and 300 per c.mm. and may fluctuate during the day and from day to day. In this paper the lowest normal level is accepted as 40 per c.mm. Values up to 400 are not considered to indicate eosinophilia.

Eosinophils (Figs. 1 to 6)

The changes in the eosinophil count after burning followed a constant pattern. Within a few hours of burning the number of circulating eosinophils was found either to be falling or to have fallen to low or zero values. The eosinopenia was maintained for a variable number of days, after which the count began to rise. Later a peak value was reached, and then the eosinophil count declined. The pattern was therefore one of *post-burn fall, period of eosinopenia, post-eosinopenic rise, and later changes.*

The Post-burn Fall

In 10 patients on whom eosinophil counts were repeated hourly or so on the day of admission, the eosinophils fell progressively from normal or supra-normal values to reach low or zero levels a few hours

later (Table II). The hourly changes in Case 7 are shown graphically in Fig. 1. In nine other patients the eosinophil levels were already low within a few hours of burning and sometimes a fall from a low to a lower level was found—for example, Cases 17 and 26.

As the eosinophil counts before burning were unknown, it was impossible (except in Case 9) to determine how soon the fall began. However, the interval between burning and the onset of a definite fall in the eosinophil count was determined in 18 patients, and was found to be within two hours in seven and within four hours in the remainder. The interval between burning and the onset of eosinopenia (defined as less than 40 cells per c.mm.) was determined in 19 patients and found to be within two hours in five, between two and four hours in eight, and after four hours in the remainder.

FIG. 1.—Serial counts on the day of burning. As the eosinophils fall to reach an eosinopenic level there is a moderate lymphocytopenia and a definite neutrophil leucocytosis (Case 7).

FIG. 3.—Serial neutrophil, lymphocyte, and eosinophil counts in Case 21.

FIG. 4.—Serial neutrophil, lymphocyte, and eosinophil counts in Case 15.

FIG. 2.—The curves show the rates of disappearance of the eosinophil cells after burning in ten patients. The 100% values are the maximum values found and are plotted at zero hour. The curves of the extensively burned shocked patients are the non-interrupted heavier lines. There is no gross difference in the rates of disappearance of the eosinophils from the blood in the different patients. Beyond about +2 hours the curves flatten to the right and represent the established eosinopenic state rather than a slowing down of cell disappearance. Note that the numerals in this and all subsequent figures refer to case numbers.

FIG. 5.—Early eosinophilia (Case 9).

FIG. 6.—Serial eosinophil counts during the first week after burning in five patients. The falling of the eosinophil count soon after burning is seen in Case 33 and then a period of eosinopenia occurs, present in all the cases. This lasts from one to seven days and is followed by a rise in the count. Below the horizontal interrupted line at 40 eosinophils per c.mm. the counts are considered eosinopenic. Note that the end of the eosinopenic stage is sometimes heralded by a small rise in the count for one or two days (Case 22).

The *rates* of disappearance of the eosinophils from the blood in 10 patients are shown in Fig. 2; the steepness of the curves gives the rates of eosinophil disappearance. Similar rates of eosinophil disappearance occurred both in the extensively burned shocked patients (heavier non-interrupted curves) and in the less-burned non-shocked patients. The rates of disappearance vary between 30% and 70% of the cells an hour.

Period of Eosinopenia

It has been shown that a rapid disappearance of eosinophils occurs within a few hours of burning and an eosinopenic state with very low or zero levels is soon established. The eosinopenia is maintained for varying periods in different patients.

The duration of eosinopenia was defined as the interval between the time of burning and the time at which the eosinophil count first reached a level of 40 per c.mm. during the post-eosinopenic rise. The latter point was often interpolated from the curve. The *true* period of eosinopenia was some hours shorter than this and the error of the calculations was within $\pm \frac{1}{2}$ day.

In 28 patients surviving this period (including two who subsequently died and another recent case not included in Table I), the duration of eosinopenia was plotted against the percentage area burned (Fig. 7). The mean periods in groups of these patients are shown in Table III (p. 982). The eosinopenia lasts about one to two days in patients with burns less than 10% in extent (mean, 1.3 days), and is longer, usually three to five days (mean, 4.0 days), in those more extensively burned. This is statistically significant, but the

FIG. 7.—Relationship of the percentage of the body area burned to the duration of eosinopenia in 28 patients (see text). † = Died.

relationship between the two variables—duration of eosinopenia and percentage area burned—is not a simple direct one. In Fig. 7 it appears to be an exponential curve, with its concavity facing to the left, rising steeply between four and six days after burning. A few points fall away from the curve, and their significance is discussed later.

Post-eosinopenic Rise (Figs. 3 to 6)

The end of eosinopenia was often heralded by a slight increase in the count, but often this was abrupt. The eosinophil concentration progressed for several days to reach a peak: sometimes the rising curve was interrupted by one or two temporary falls, occasionally to an eosinopenic level, and then rose again to a greater height (Fig. 3).

The heights of the peaks varied considerably ; in 13 patients they were between 70 and 250 cells per c.mm., and in eight others values between 350 and 500 were found. Such temporary high borderline values cannot be regarded as a true eosinophilia, but are probably due to the rebound phenomenon often found when retardation is succeeded by a relative absence of restraint.

However, in four patients abnormally high levels were found, termed "early" eosinophilia.

Early Eosinophilia in Burns (Fig. 5)

In two children (Cases 5 and 9) an eosinophilia preceded the fall to eosinopenia (Table II), and the post-eosinopenic rise was exaggerated into what may be termed an acute attack of eosinophilia, which also occurred in two other children (Cases 8 and 14). The maximum counts were 693, 981, 2,360, and 1,875 (5%, 8%, 23%, and 20% of the total leucocyte counts), and the eosinophilia lasted 6, 10, more than 14, and 8 days respectively.

In Case 5 an acute otitis media was diagnosed the day before the onset of the post-eosinopenic eosinophilia. In Case 9 (Fig. 5) the onset of this eosinophilia coincided with a generalized erythema sparing the face, a pyrexia of 104° F. (40° C.), and a one-day neutrophil peak of 15,000 per c.mm.; group A haemolytic streptococci were isolated from the throat and burned skin. No intercurrent infection was noted in the other children.

Later Eosinophil Changes

After the peak rise the eosinophil level usually declined, but remained within normal limits. In some severely burned patients the eosinophil count remained low for two to four weeks as if adrenocortical hyperactivity was continuing (see below). In many patients sudden but temporary falls in the eosinophil level occurred, often related to a surgical operation or to infection.

Late Eosinophilia in Burns

In five patients eosinophilia occurred four to six weeks after burning. In Case 5 early eosinophilia was found, but during the next five and a half weeks the eosinophils did not exceed 350 per c.mm. However, the count rose to 484 per c.mm. on the 40th day, was 840 five days later, 1,431 on the 49th day, forming 11% of the total white cell count, and before discharge on the 52nd day was 1,256 per c.mm. In Case 14 early eosinophilia occurred, after which the eosinophil count subsided, and then on the 27th and 30th days values of 601 and 606 per c.mm. were found. Case 13 did not have eosinophilia until the 40th day, when the count was 710 per c.mm. (6% of total leucocytes), and the eosinophilia persisted, with maximum counts of 1,100 per c.mm. on the 47th and the 48th days, until the 56th day, after which the level fell to normal. In Case 19 eosinophilia began on the 33rd day, when the level was 500 per c.mm., and this continued for 12 days. In Case 27 eosinophilia began on the 43rd day, when the count was 580 per c.mm., and persisted for about a week.

Twenty patients remained in hospital longer than 21 days, and 15 more than 28 days. As this eosinophilia is delayed until four to six weeks after burning, its true incidence was 5 out of 15 or 20 patients (25 or 33%).

We do not know the aetiology of late eosinophilia, but it may be due to sensitization to a drug used in treatment.

Lymphocytes

In six patients two or more lymphocyte counts within a few hours of burning were performed, and two children showed a marked fall from high levels. For example, in Case 5 the count of 9,700 per c.mm. at one and one-quarter hours after burning fell to 4,500 and 2,500 at two and three hours. In three patients a smaller fall was observed—for example, Case 7 (Fig. 1). In other patients low lymphocyte counts during the first day or two were followed by higher counts on succeeding days (Figs. 3 and 4), suggesting that an early lymphopenia was present.

Therefore, a lymphopenia commonly occurs after burning; it may be marked in some children, but is usually moderate and lasts only a day or two. Subsequently, the lymphocyte level varied considerably: a lymphocytosis sometimes accompanied the post-eosinopenic rise or the secondary neutrophil wave.

Neutrophils

The Primary Neutrophil Wave (Figs. 1, 3, 4, and 5).—It is well known that a neutrophilia follows burning (Locke, 1902; McIver, 1933; Brown, 1944); in this study this was confirmed and is called the *primary* neutrophil wave. The onset of the leucocytosis was rapid; commonly the count was high within a few hours of burning and was always at its maximum within 24 hours, often within the first few hours. Then the count fell, usually rapidly at first, to normal levels on the

second to the fourth day, so that the primary wave lasted from one to three days. In three patients, for example Case 15 (see Fig. 4), the count fell, but remained high for four to six days after burning, rising again as the secondary neutrophil wave set in. The height of the primary wave was related to the extent of the burning—for example, in five of the eight patients with less than 10% burns the maximum counts were between 10,000 and 15,000 per c.mm., and in eight of the ten more extensively burned patients studied the maxima were more than 20,000 per c.mm. The highest counts recorded, which never exceeded 40,000 per c.mm., all occurred in severely shocked patients. Primary neutrophilia did not occur in two patients with burns less than 10% in extent (Case 6; Case 9, Fig. 5).

The Secondary Neutrophil Wave (Figs. 3, 4, and 5).—In 13 of the 16 patients investigated a definite or marked increase in the neutrophil count began five to ten days after burning even if a primary wave did not occur (Fig. 5). The count increased to a maximum and then declined to a normal level two to fourteen (usually three to eight) days later. This leucocytosis did not occur in three of the eight patients with less than 10% burns; in four others the maximum counts were below 13,000 per c.mm. The secondary waves were usually higher in the more extensively burned in whom they were always found, and the maximum counts were usually more than 15,000 per c.mm. The secondary rise of leucocytes has been observed by Brown (1944), who considered that it was probably due to infection of the raw burned surfaces. The bacteriology of the burned skin in our series throws no light on this.

Discussion

Eosinopenia and Adrenocortical Hyperactivity in Burns

Among the effects of A.C.T.H. and 11-oxysteroids is a fall in the eosinophil count associated with a degree of lymphocytopenia and neutrophil leucocytosis (Thorn *et al.*, 1947a; Dougherty and White, 1947; Hills *et al.*, 1948; Forsham *et al.*, 1948). The same blood changes taking place after burning suggest that adrenocortical hyperactivity occurs in the burned patient, and the association of a more prolonged eosinopenia with more extensive burns suggests that the hyperactivity is more prolonged in these patients.

Other evidence supports this contention. Many of the effects of burning resemble those of administration of A.C.T.H. or adrenal steroids. Sodium and chloride retention and increased potassium loss occur both during the first few days after burning (Moore *et al.*, 1950) and after injection of A.C.T.H. or deoxycortone (Prunty *et al.*, 1948; Forsham *et al.*, 1948): similar disturbances of carbohydrate metabolism, including hyperglycaemia, sometimes glycosuria, and lactic acid acidemia, occur in experimental burns (Clark and Rossiter, 1944), human burns (Taylor *et al.*, 1944), and after the administration of A.C.T.H. or cortisone (Forsham *et al.*, 1948; Conn *et al.*, 1949; Sprague *et al.*, 1950), and the hyperglycaemia in rats after burning can be prevented by previous adrenalectomy (Clark and Rossiter, 1944).

Similar changes in nitrogen metabolism, such as increased nitrogen excretion, follow burns (Cope *et al.*, 1943; Levenson *et al.*, 1945; Keyser, 1948; Moore *et al.*, 1950) and occur after the administration of A.C.T.H. and 11-oxysteroids (Long *et al.*, 1940; Sprague *et al.*, 1950). Degenerative changes in lymphoid tissue occur after burning (Bardeen, 1898; Baker, 1945) and after injection of A.C.T.H. (Dougherty and White, 1947).

There is an increase of the urinary excretion of 17-ketosteroids (Cope *et al.*, 1943) and of biologically active reducing glyco-corticoids (Heard *et al.*, 1946) after burning and after injection of A.C.T.H. in the intact animal or man (Thorn *et al.*, 1947b; Venning *et al.*, 1948; Prunty, 1950; Sprague *et al.*, 1950). The ascorbic acid content of the adrenals in the rat (Clark and Rossiter, 1944) and of the blood in man (Abbott *et al.*, 1946) falls after burning, and a similar adrenal depletion occurs after the administration of A.C.T.H. (Long, 1947; Sayers and Sayers, 1949). Again, the cholesterol content of the adrenal in rats is decreased both after burning and after A.C.T.H. (Long, 1947).

We may therefore conclude that the adrenal cortex is actively stimulated in burns through an increased production of A.C.T.H. by the pituitary.

Hypothalamic Control.—De Groot and Harris (1950) have shown that the adrenocorticotrophic secretion of the anterior pituitary in rabbits is under hypothalamic control, and Hume and Wittenstein (1950) draw a similar conclusion from their work in dogs. Hume and Wittenstein also showed that the hypothalamus can be activated by nervous impulses from an injured area, and this is obviously of significance in burns.

Adrenocortical Failure in Burns

We may therefore infer that if a lesion develops in the hypothalamus, pituitary, or adrenal it may have the same effect on adrenocortical activity—that is, the adrenal cortex may fail to function. The term “adrenocortical failure,” which will henceforth be used in a functional sense, does not necessarily imply that the fault lies in the adrenal itself, although this may be so.

It is important, therefore, to determine whether adrenocortical failure occurs and can be diagnosed in some burned patients, as “replacement” therapy with A.C.T.H. or cortisone may then be indicated.

The Eosinophil Changes in Fatally Burned Patients (Fig. 8)

If acute adrenocortical failure occurs in some burned patients its incidence is probably greater among those

who later succumb than among those who survive. An analysis of the eosinophil changes in eight fatal cases was therefore made with this in mind.

One of these patients died four hours after burning while the eosinophil count was falling, and four others died two to three days after burning during the established period of eosinopenia. Such changes, we believe, are due to hyperactivity of the adrenal cortex. In the remaining patients the possibility of adrenocortical failure arose.

In Case 28 the eosinophil counts $1\frac{1}{2}$, 2, and $2\frac{1}{2}$ hours after burning were 257, 276, and 268 per c.mm. respectively, and the patient died 15 minutes after the last count. The failure of the count to fall does not exclude the possibility that eosinopenia may have occurred later had he lived long enough. In support of this, the post-mortem histology revealed large numbers of eosinophils in the spleen and moderate numbers in other organs. This may indicate the removal of eosinophils from the peripheral blood, as similar changes have been noted in other patients dying within 24 hours of burning (unpublished observations). On the other hand, the patient presented some evidence of Cushing's syndrome—namely, obesity, bilateral lipoid-laden, hypertrophic, and convoluted adrenal cortices (together both glands weighed 30 g.), a pituitary in which the basophils were numerous and eosinophils few in number, a cystic thyroid, a fatty liver, and sclerosis of the vessels of the liver, kidney, and other organs. In this patient, therefore, the burning may have been unable to produce the normal response from the abnormal pituitary and adrenal glands, but the evidence was inconclusive.

In Case 29 the eosinophil count was zero at 12 and 14 hours after burning, suggesting early hyperactivity of the adrenal cortex. Shock and haemoconcentration were treated with 6 litres of dextran and 0.5 litre of blood. A transient haemoglobinuria was noted three hours after burning, and oliguria developed at nine hours. At 30 hours the patient's temperature suddenly increased to 104°F . (40°C .), pulse 120, and respirations 50. At 38 hours the eosinophil count was 11 per c.mm., and two hours later this had risen to 99. The eosinopenic period lasted therefore only one and two-thirds days. From Fig. 7 a period of four to five days with this extent of burning would have been expected—that is, a “premature” rise in the eosinophils took place. At this time the patient was very ill, her respirations were still 50 a minute, she was very restless, and her extremities were cold: two hours later she died suddenly, and the possibility of acute adrenocortical failure arose, possibly due to hypothalamic changes.

Unfortunately permission for a necropsy was refused, but blood removed from the heart 30 minutes after death gave a count of 127 eosinophils per c.mm. and confirmed the “premature” post-eosinopenic rise. In addition, the lymphocyte count was 4,700 per c.mm. (total leucocytes, 18,000 per c.mm., neutrophils, 71%), and in support of adrenocortical failure was a relatively low blood glucose of 80 mg. per 100 ml. The relatively low plasma sodium of 300 mg. per 100 ml. and very high plasma potassium of 36 mg. per 100 ml. (the plasma was separated soon after collection of the blood and showed no visible haemolysis) could support such a diagnosis, but the oliguria complicated the problem.

In the eighth case (Case 32) eosinopenia was established within two hours of burning, lasted four and a half to five days, when the rise in blood eosinophils

FIG. 8.—The eosinophil changes in eight fatally burned patients. The arrows indicate time of burning, the daggers times of death. Hours (or days)=hours (or days) after burning.

occurred, and the patient died on the ninth day. From an analysis of the clinical symptoms, blood changes, and post-mortem findings the evidence for adrenocortical failure was inconclusive.

Therefore the eosinophil changes in five out of eight fatal cases suggested that hyperactivity of the adrenal cortex was present before death: in another patient there was evidence suggesting that adrenocortical failure had occurred, and in two others the evidence was inconclusive.

Steroid Therapy in Burns

Deoxycortone acetate and extracts of the adrenal cortex have been used therapeutically in burns (Wilson *et al.*, 1936, 1938; Einhauser, 1939; Elkinton, 1939; Ivory, 1940; Scudder, 1940; Cope *et al.*, 1943; Rhoads *et al.*, 1943), but the results reported by different workers are not consistent. Beneficial results have been claimed but are often difficult to evaluate and sometimes not impressive; nevertheless some dramatic recoveries have been reported. However, the purified glyco-corticoid hormones of the adrenal were not then available. More recently Crassweller *et al.* (1950b) supplemented the treatment of three burned patients with cortisone. Two died and the survival of the third may or may not be related to the use of cortisone. Crassweller and his colleagues (1950a) claimed to have lowered the death rate from a standard experimental burn in mice by treatment with a special extract of normal urine prepared in such a way that it was likely to contain cortisone. Their results, which are suggestive, are not, however, conclusive, as certain experimental precautions, notably the control of environmental temperature, were not taken.

Hyperactivity and Failure of Adrenal Cortex and the Period of Eosinopenia

I have shown that eosinopenia develops after burning and have produced evidence which indicates that this is a sensitive reflection of adrenocortical hyperactivity; furthermore, I have found that the duration of eosinopenia is related to the percentage area burned (Table III).

TABLE III.—A Comparison of the Mean Durations of Eosinopenia in Groups of Patients with Burns of Different Extent

	Body Area Burned				
	0-10%	11-20%	21-30%	>30%	>11%
No. of patients	9	8	4	7	19
Mean duration of eosinopenia in days	1.3	4.0	4.4	3.8	4.0
Standard deviation	0.66	0.95	1.7	1.3	0.98

A statistical comparison of the mean durations of eosinopenia in the 0-10% and >11% groups shows a highly significant difference ($t = 5.712$, $p < 0.001$).

In Fig. 7 the points of four patients (Cases 13, 22, 27, 29) fall well to the right or well above the correlation zone, and the question arises whether these variations are within "normal limits" or if they represent departures from the normal. In Case 13 (12% burn) the burn shock was greater than was expected from the extent of burning; in Case 22 (26% burn) the area burned did not reflect either the severity of burning (one limb was charred and had to be amputated) or the severe degree of clinical shock. If the period of eosinopenia measures the duration of the adrenocortical reaction to burn stress, and the percentage area burned is merely an index of the stress present, then the "prolonged" eosinopenic periods in these two patients can

be accounted for. Similarly in Case 27 (36% burn) burn shock was present, but was not severe and was easily controlled. On the other hand, if the period of eosinopenia is appreciably shorter than that expected from the area burned—i.e., if a "premature" post-eosinopenic rise in the eosinophils occurs—adrenocortical failure may be suspected, particularly if the patient is at the same time seriously ill. Case 29 was such a patient.

Summary

The quantitative changes in the eosinophil counts in 35 patients, and of the lymphocyte and neutrophil counts in 18 patients, with burns of various degrees of severity have been studied. Soon after burning, the eosinophil count falls and reaches low or zero values in a few hours; this is often accompanied by a lymphocytopenia and usually by a neutrophil leucocytosis (primary wave).

The eosinopenia, which may persist for a few days, lasts longer in the more extensively burned patients. In four patients an early eosinophilia was found, and in two it was associated with intercurrent infection. In five patients a delayed eosinophilia began four to six weeks after burning.

The height of the primary neutrophil leucocytosis generally increases with the percentage area burned. A further neutrophil leucocytosis (secondary wave) develops five to ten days after burning.

The significance of eosinopenia in burns is discussed in the light of the known biological and metabolic effects of burning and of the recent knowledge of A.C.T.H. and cortisone. It is suggested that the eosinopenia is a sensitive index of adrenocortical activity in burns.

The possibility that adrenocortical failure may occur in some burned patients is raised, and it is suggested that a "premature" rise in the eosinophil count in relationship to the percentage area burned may help in such a diagnosis.

The eosinophil changes in five out of eight fatally burned patients suggested that in them hyperactivity of the adrenal cortex was present before death. In one other there was some evidence for adrenocortical failure.

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SOME OBSERVATIONS ON SURVIVAL OF PATHOGENIC BACTERIA ON COTTON-WOOL SWABS

DEVELOPMENT OF A NEW TYPE OF SWAB

BY

SYDNEY D. RUBBO, M.B., Ph.D., Dip.Bact.

AND

MARY BENJAMIN, B.Sc.

(From the School of Bacteriology, University of Melbourne)

This inquiry was prompted by our doubts on the reliability of culturing swabs when examination had been delayed by sending the specimens through the post or by depositing them after laboratory hours. Our laboratory is often obliged to carry out such delayed examinations, but similar delays must be fairly common in hospital and public health bacteriology. Apart from a few isolated statements, little attention has been given to the question of survival of the common pathogenic organisms on cotton-wool swabs.

The earliest account describing the use of cotton-wool swabs in clinical pathology appears to have been given by Councilman (1893), who recommended their employment in the bacteriological diagnosis of diphtheria. About this time Continental and English workers were using a variety of bizarre methods. For example, in France, Roux and Yersin (1890) described the use of a platinum wire flattened at the end for sampling from diphtheritic membranes. Goldscheider (1893), in Germany, used a platinum scoop; Hamilton (1895), working in London, suggested a goat's-hair

brush; Hardman (1895) preferred to collect the discharges on a white paper which could then be dried before a fire and sent to the laboratory by post. Preston (1896) and Hewlett and Nolan (1896) were among the first English bacteriologists to recommend the use of cotton-wool swabs for the isolation of diphtheria bacilli. By 1900 swabs were in common use (Kolle and Wassermann, 1903).

Although 50 years have now elapsed the bacteriologist can still give the clinician or the field investigator little information about the survival time of common pathogens on these simple appliances. It is generally agreed that the bacteriological examination should be done as soon as possible after swabbing; but this vague recommendation, however conservatively it might be interpreted, cannot always be met in practice. Van Reimsdijk (1924) studied the survival of diphtheria bacilli on swabs and found that by inserting the swab in a serum-agar gel contained in the holder tube the survival of these organisms was assured for 24 hours at room temperature. This method was cumbersome and has not been adopted. Brahdý *et al.* (1934) suggested dipping swabs in serum and incubating for four hours before culture and direct smear. Parish (1935) made a similar recommendation, but both these investigators were interested in developing a rapid method of diagnosis of diphtheria and not in extending the survival time of the organism on the swab.

Downie (1940) investigated various methods of prolonging survival of meningococci on nasopharyngeal swabs, and found that these organisms could be cultured 24 hours after swabbing, provided the swab was placed in contact with a blood-agar medium contained in the swab tube. Hynes (1942) stated that rectal swabs carrying intestinal pathogens should be cultured very soon after collection, or, if not, the swab should be kept moist by immersion in saline agar. Mitchell *et al.* (1946) described an elaborate method of prolonging survival of haemolytic streptococci, impossible for routine use, and Saint-Martin (1949) stated that gonococci would survive 4 to 18 hours on swabs if the latter were thrust into Hirschberg's medium immediately after swabbing. More recently, Aycock and Mueller (1950) recommended immersion of the swab in sterile horse blood for recovery of meningococci on delayed plating. Finally, none of the current textbooks in bacteriology or clinical pathology give any indication of the time limits for delayed culture of swabs.

It is evident from this survey of literature that this important problem requires further elucidation so that the results of delayed culture from swabs can be interpreted with some degree of certainty.

Laboratory Results

Two rather slight observations served as a starting-point of the present study. First it was noted that the survival time of *Str. pyogenes* on swabs from infected wounds was far greater than on throat swabs carrying the same organisms. The second observation was that 24-hour-old throat swabs mounted on wire were often discoloured by solution of the iron in the presence of saliva. The lines of investigation which followed soon showed that the former was a more fruitful approach to the problem of survival than the latter, which, however, could be easily overcome by discarding wire applicators for wood.