Section of Pathology

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DISCUSSION: PATHOLOGICAL SEQUELÆ OF BURNS

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Local Vascular Changes in Burned Skin

Clinically the local inflammatory changes after burning are manifest by redness and swelling of the skin. This communication is concerned with the increased permeability of the dermal capillaries and the changes in their blood flow.

Outline of methods.—Full details have been given elsewhere (Sevitt, 1949*a*, 1949*b*). Circular burns, 1 in. in diameter and of known temperature and duration were made with a constant temperature burning iron usually on the shaven abdomen of albino guinea-pigs. The animal's plasma was dyed by the injection of Evans blue or Brilliant Vital Red. Coloration of the burned skin is due to leakage of plasma albumin and indicates an increase of dermal capillary permeability (Fig. 2).

The least severe burns causing an increase of permeability.—In burns of the same duration, the appearance of dye occurs at and above a minimal burning temperature. For example (Fig. 1) in

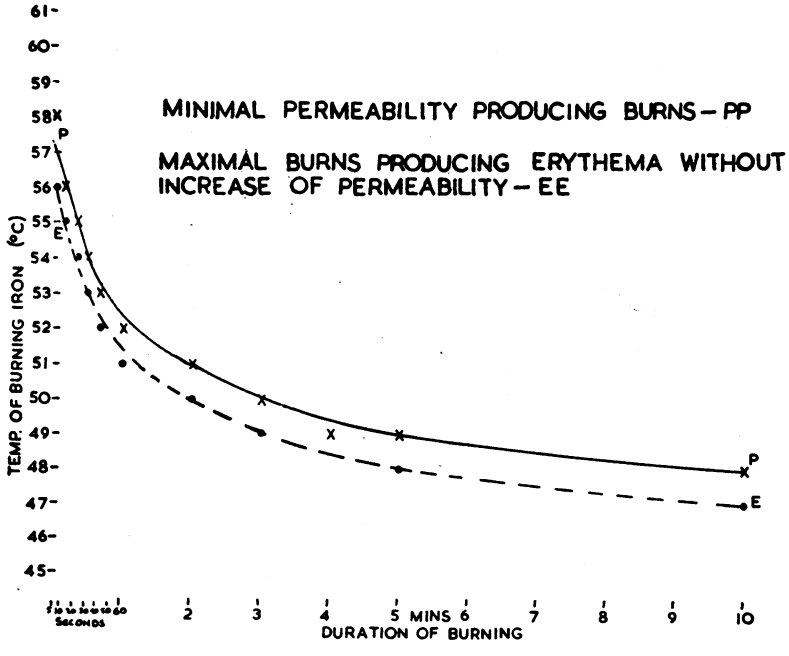

FIG. 1.—The minimal temperatures and periods of application of the burning iron which just produce an increase of permeability in the dermal capillaries. At and above curve PP an increase of permeability occurs; at and below EE erythema is the only evidence of burning. The curves were made by making many burns above, at and below the points recorded.

burns lasting 60 seconds this is 52° C., in five-minute burns it is 49°. Above curve PP an increase of permeability occurs, below EE erythema is the only visible evidence of burning. By extending PP to the right to obtain an infinitely prolonged burn, the lowest burning temperature which produces an increase of permeability is about 45°.

Dermal threshold temperature.—The temperatures in PP are those applied to the surface of the skin: during burning the temperatures in the dermis must be lower than these. By correlating the subdermal temperatures recorded during burning by Mendelssohn and Rossiter (1944), it has been shown that different burns, all of which just produce an increase of permeability, also produce similar subdermal temperatures. Thus the burn at 54° for 30 seconds produces a subdermal temperature of 41° to 44° in different animals: similarly, burning at 52° for 60 seconds produces a subdermal temperature of 41° to 45°. This suggests that a threshold temperature exists to which the dermal capillaries must be heated before they leak abnormally. In the prolonged burn at 45°, the subdermis reaches 41° to 42° and therefore within the range of 41° to 45° is the threshold temperature for increase of permeability.

Delayed increase of permeability and delayed œdema.—When Evans blue is injected before burning it usually stains the burned skin within a few minutes of burning. In less severe burns the dye may not appear for 30 to 60 minutes or longer. Experiments involving the injection of dye after burning, have shown that the delayed appearance of dye in these burns is mainly due to a delayed leakage of dye from the capillaries. By estimating the water content of burned skin, it has been shown that several hours' delay in œdema formation occurs in many burns. In severer burns, delayed permeability change and œdema formation occur in the subcutaneous tissues. The cause of this delayed permeability is obscure. It may be due to the diffusion of cell products released superficially and acting on the deeper capillaries but histamine release is not responsible (*vide infra*). Alternatively nervous influences may play a part. A fuller account of these experiments will be reported later.

Burns on denervated skin.—Does the permeability response on denervated skin differ from that on normal skin? Unilateral abdominal palsy and an area of anæsthetic abdominal skin was produced in guinea-pigs by unilateral section of the lower 1 or 2 thoracic and the upper 3 or 4 lumbar spinal nerves. Weeks later, Evans blue was injected and similar burns were made on the analgesic skin and on anatomically similar sites of the normal skin.

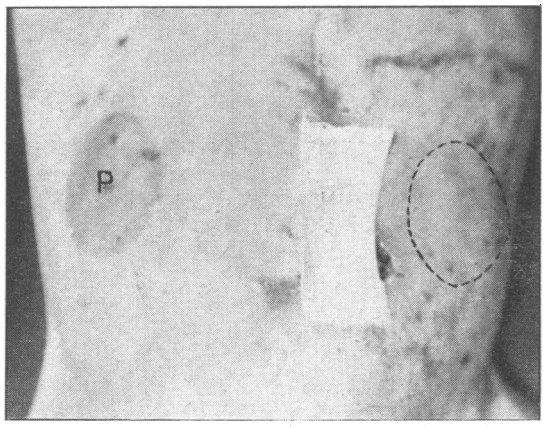

FIG. 2.—Burning denervated skin. Right-sided abdominal anæsthesia and palsy were produced in guinea-pigs by unilateral section of the thoracolumbar spinal nerves. Two months after operation similar burns were made on the right (anæsthetic) and left sides of the animal after intracardiac injection of Evans blue. In the photograph showing part of a guinea-pig's back, the results of two burns are recorded. The anæsthetic skin is outlined by skin pencil. The burn on the left side produced a circular blue patch of skin (P) corresponding to the site of application of the burning iron, indicating increased permeability of the dermal capillaries. However, dye did not appear in the homologous burn on the right side, the site of which is outlined by dots.

Many of the minor burns on the denervated skin did not produce a permeability change although similar burns produced the blue patches of increased permeability on the normal side of the animal (Fig. 2). In less minor burns, the permeability reactions were slight or indefinite on the denervated side but were definite on the normal side. Severer burns produced indistinguishable permeability reactions on both sides of the animal.

Analysis of the results showed that the time-temperature curve of the minimal burns producing a permeability increase on denervated skin lies at a level 2° to 3° higher than the curve for burns on normal skin (Fig. 3).

The difference between normal and denervated skin is due either to a raising of the permeability threshold temperature of the denervated dermis so that the dermal vessels cannot leak until a higher temperature is reached in the dermis; or alternatively to a lowered heat conductivity of the dermis so that a higher burning temperature is required to attain the normal dermal threshold for an increase in permeability.

Capillary stasis in burned skin (Sevitt, 1949*a*).—Many burns which show a permeability reaction to dye injected before burning, or some time after burning, show the reaction of stasis when the dye is injected later. A narrow coloured ring representing graded vascular damage surrounds the burn, but the site of application of the burning iron remains erythematous and does not blanch on pressure. Continuation of the dermal blood flow or development of statis within a period was demonstrated by the introduction of the red and blue dyes at different times—the double dye technique—and thus, the time limits of stasis involving the whole depth of the dermis were found. Stasis may set in hours, minutes or seconds after burning, the interval decreasing as the severity of burning increases until it develops within the burning period.

A dermal threshold temperature for stasis was postulated by correlating the minimal burning temperatures producing stasis (in burns of known duration), and the temperatures reached in the subdermis during burning. To produce stasis about four hours after burning, the dermis must reach a temperature of 47° to 48° during burning.

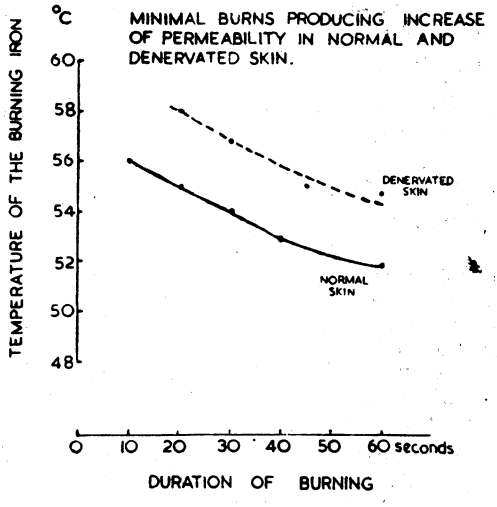

FIG. 3.—The minimal temperatures and periods of application of the burning iron which just produce an increase of capillary permeability in the denervated skin of the guinea-pig, compared to the minimal burns producing permeability increase on the normal side of the animals. The curve of burns on the denervated skin lies 2 degrees to 3 degrees higher than the burns on the normal skin.

Failure of antihistamine drugs to influence the local vascular changes.—The drugs Benadryl, Antistin and Anthisan were used in full, non-toxic dosage. Similar sets of burns varying in severity from minor to stasis-producing burns were made on antihistaminized and control guinea-pigs. Burn for burn similar permeability reactions or reactions of stasis occurred in the two sets of animals (Sevitt, 1949*b*). A burning experiment was performed on human volunteers, 4 taking Antistin and 4 taking dummy tablets. The inflammation, as measured by the clinical œdema and blistering produced, as well as the protein content and cellular exudate in the blister fluid, varied to the same extent in the volunteers taking Antistin as it did in the controls (Sevitt *et al.*, 1952). It was concluded that histamine release is not responsible for the inflammation in burned skin.

Cortisone.—In the guinea-pig experiments so far performed, similar dye reactions, burn for burn, have occurred in the controls and in the animals receiving cortisone, and quantitative skin water experiments indicate that cortisone has little, if any, influence on the degree of post-burn œdema.

Preliminary experiments with rabbits probably confirm the failure of cortisone to influence the permeability changes after burning but possibly indicate that cortisone may delay the onset of capillary stasis in the dermis. These experiments are not yet completed.

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The Endocrine Response to Burning Injury

When cortisone and adrenocorticotrophic hormone (ACTH) became available, interest was aroused in the adrenocortical response to burns. By way of introducing this subject, we may review evidence for the release of adrenaline and ACTH, and I shall mention recent observations which broaden our ideas of the endocrine response to injury.

The adrenaline response of the adrenal medullæ.—Although this response has not been measured directly in burned patients—nor, for that matter, has any endocrine response—its occurrence is generally accepted. There is supporting evidence that fright and pain cause the release of adrenaline in animals (Elliott, 1912; Cannon, 1915). Other investigators have observed rises of blood pressure and blood sugar in burned animals; these changes can be attributed to adrenaline (Johnson and Blalock, 1931; Lambret and Driessens, 1937).

The adrenocorticotrophic (ACTH) response of the anterior pituitary.—Adrenaline released after burning may have a role in the release of ACTH from the anterior pituitary. McDermott *et al.* (1950), and Recant *et al.* (1950) have presented persuasive evidence that a rise in the level of circulating adrenaline causes an adrenocortical response mediated by the anterior pituitary.

The adrenocortical response.—A large number of steroids have been extracted from the adrenal cortex but Nelson *et al.* (1950) and Pincus *et al.* (1951) using perfused isolated mammalian adrenals find that ACTH causes the release principally of 11–17 hydroxycorticosterone (Hydrocortisone, Kendall's compound F.).

The effect of 1 gramme of this steroid given in diminishing daily doses over four days to a healthy young volunteer was investigated. He was kept lying in bed, immobilized in burn dressings. Compared with three control days there were: a prompt and profound fall of circulating eosinophils; increased daily urinary excretions of formaldehydogenic corticoids and 17-ketosteroids; decreased glucose tolerance; markedly positive sodium balance and negative potassium balance; less obvious fluid retention and increased urinary nitrogen excretion. (For methods, *see* Evans and Butterfield, 1951). These results confirm the findings of Fourman *et al.* (1950) and Conn *et al.* (1951).

The similarity between the effects of 11–17 *hydroxycorticosterone and those observed after burning injury.*—There was a close similarity between these effects of diminishing doses of 11–17 hydroxycorticosterone and measurements made after burning injury. Indeed, this resemblance was close both as to magnitude and timing when the results of the foregoing study were compared with measurements made during the first eight days after injury in a 30-year-old man who suffered a 30% burn. This patient showed an early profound depression of circulating eosinophils, and similar patterns to the volunteer as regards corticoid and 17-ketosteroid excretion, sodium and potassium balance and glucose tolerance. The findings with fluid and nitrogen balances were not so close, although, of course, the interpretations of all balance studies were complicated by treatment.

These investigations, and those in 18 other burned patients, suggest that there is an adrenocortical-like response to thermal injury, and that this could play an important part in producing many of the metabolic alterations seen in burned patients. Whether this response is due to increased adrenocortical activity or to decreased conjugation of adrenal steroids by the liver, or both, is not known.

The variation in the magnitude of the adrenal response with the extent of burn.—Analysis of the results over the first ten days after injury in 19 patients, of ages 4 months to 76 years and burns of 2–60%, showed highly significant correlations between the percentage body burned and the mean eosinophil count ($R = -0{\cdot}69$) and the mean daily corticoid excretion ($R = 0{\cdot}58$). The most plausible link between these variables is adrenal function. It would therefore seem that the extent of the burn affects the degree of adrenocortical response. The data from balance studies show the same trend, but are less amenable to mathematical analysis because of differences in treatment, age and sex.

Other endocrine responses.—Our day-by-day findings in the 19 burned patients suggest that endocrine systems other than the adrenals are involved. Theobald and Verney (1935) have shown that antidiuretic hormone is released after painful stimuli, and Barac (1946) has presented evidence for circulating antidiuretic substance in the blood of burned dogs. An antidiuretic response is probably an important factor after burning injury, and would explain discrepancies between electrolyte and fluid balance. Selye (1951) believes that growth hormone (S.T.H.) is released in response to injury, and causes the adrenal cortex to elaborate salt-retaining, desoxycorticosterone-like, steroids. Observations in one patient suggest that there was an increase of such steroids in the urine for a few days after injury. This mechanism would account for anomalies of electrolyte balance and of glucose tolerance. Romani (1952) reports that burning injury is followed by a thyrotrophic response, but Cope *et al.* (1952) have been unable to confirm this in burned patients.

Conclusions

A study of burned patients strongly suggests that there are endocrine responses in the first week after burning injury. Although adrenocortical effects predominate, and vary with the extent of burning, there are reasons to believe that other endocrine systems are activated.

Now that powerful hormone preparations are available, the question arises as to whether the clinician should attempt to alter, or augment these endocrine responses. This should depend upon evidence of a faulty endocrine response; it should be borne in mind that death occurs from Cushing's disease as well as Addison's disease, from water intoxication as well as dehydration.

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Fluid and Electrolyte Exchange in Burns

The basis of the main disturbance of fluid and salt balance in the burned patient is the increased permeability of the damaged local capillaries. This breakdown of the semipermeable barrier between the circulation and the remainder of the extracellular fluid results in an escape of fluid some of which collects in blisters, some leaves the body from raw surfaces and some collects in the extracellular space as œdema. In animal experiments it has been shown that a 50% burn may cause a loss of approximately one plasma volume of fluid (Leach *et al.*, 1943). Also, in experiments in which burned and unburned parts of the body were weighed, it has been demonstrated that the loss is primarily local into the burned tissues; the unburned tissues may even become lighter as a result of transfer of extracellular fluid. Corresponding to this the lymph flow from the burned limb increases in quantity and changes in composition from a low protein to a high protein content—approximately three-quarters of the normal plasma level. The exudate also contains its full complement of plasma electrolytes.

In the treated human patient further changes result from treatment. The loss of circulatory volume initially may be compensated by vasoconstriction but if, as in severe burns, leaking continues uncorrected, the diminished blood volume will cause tachycardia, hypotension and, if allowed to progress, death. Treatment with plasma or other appropriate colloid solution corrects hæmoconcentration and blood volume but to maintain this correction therapy must be continued so long as the leak lasts. This means that the volume of extracellular fluid is much enlarged, an effect which will be accentuated if much extra water or saline is used in treatment. Even when giving plasma the volumes required to maintain normal hæmatocrit values are of the order of a whole circulatory volume for a 40% surface area burn.

In view of these considerations and the dangers of overloading the extracellular space (Cope and Moore, 1947) the following appear to be rational principles of therapy:

(1) Colloid solution with full electrolyte complement, regulated in quantity by correction of hæmoconcentration, should be given to replace exudate and œdema. Reconstituted plasma has a protein concentration of about 5% which is close to the level in exudate. In view of the concurrent loss of red cells it is probable that this regime results in an under-correction of circulatory volume.

(2) Water and perhaps a small amount of salt are required to provide for losses by respiration, normal skin and urine. This total is of the order of 2–3 litres per 24 hours.

Further to this major exchange of fluid due to altered capillary permeability, there is some passage of sodium into the damaged cells and loss of potassium from them, but it is probable that the quantities involved are relatively small (Moore *et al.*, 1948).

One of the features of renal function following severe burns is a tendency to oliguria. In a recent study Dr. N. W. J. England and I have found that about 500 ml. urine per day can fairly easily be obtained during the first few days, but that neither increase of colloid input within orthodox limits nor moderate increases of sodium or water input can greatly increase this flow. This is particularly true of large burns. Many small burns do respond by excreting extra amounts of fluid given and a corollary is that if the urine output is good then fluid management is almost certainly satisfactory; but we have not had these high flows with the larger burns and have rather come to accept an oliguria of about 500 ml./day as a reasonable optimum. No great urea retention occurs with such flows, and any slight rises are subsequently quickly corrected. Our finding of good renal concentration in this series of cases did not suggest that tubular necrosis was present, and we consider that with modern treatment this is probably a rare complication. During the period of oliguria renal sodium retention usually occurs and studies have been made of the time and circumstances of onset and cessation of this retention. Serum sodium level characteristically declines during the period of retention and rises again after release.

Potassium exchange shows a relatively simple picture of sustained moderate renal output during the first few days resulting in slight negative balances if little potassium is given. The negative balance is readily corrected when full feeding commences a few days later. Serum potassium concentrations are, in the treated case, usually within normal limits. Abnormally high levels after burning appear to be rare; a commoner occurrence is a depressed serum level at about the fourth day if input has not by then recommenced.

The fluid and salt disturbance in burns is part of a general process in which local pathology and circulatory, renal and endocrine responses are involved. Many of the interrelations, particularly those concerned with circulatory volume changes, need further study.

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The Fate of Red Cells following Burns

The results, to be published elsewhere, on about 50 burns involving 5–60% of the body surface have served to emphasize the common hæmatological findings and the pathological processes that seem worthy of further investigation.

Simple budgeting of volumes of blood transfused and levels of the peripheral hæmoglobin or red cell count provided a crude picture of the degree of "red cell loss" at different stages of a burn. The average results were: from admission to first operation 38%; at excision and grafting operations 125%; between operations less than 20%; after operations less than 5%.

To the pathologist the most interesting "red cell loss" occurs from admission to the first grafting operation (usually two to three weeks). In this Unit the common practice during this time is to give a single blood transfusion equal to 40% of the blood volume. Isolated cases required repeated large blood transfusions. It is this rare type of case that has been most frequently reported in the past. It was not clear to us whether this single transfusion of 40% of the blood volume was required immediately after burning, or only when anæmia had developed. The patients investigated therefore included 12 given blood "early" in the shock stage, and 12 clinically comparable cases given blood "late" when the hæmoglobin had fallen to 80% or less of the expected normal for the age. Patients receiving blood "early" and "late" were found to be similar as regards the volumes of blood transfused and the peripheral red cell count at the time of operation. The calculated "red cell loss" was therefore also similar. The essential difference was that the patients transfused "early" went through a stage of a higher than normal red cell count, while those transfused "late" went through a stage of peripheral anæmia.

Plasma volume studies have been made using Evans blue, and red cell volume studies (32 tests) using the Ashby, or, less frequently, the P^{32} method. The cause of the red cell loss was not a rise in plasma volume (10/10 plasma volume studies normal or below normal at the time of anæmia) but a fall in red cell volume (14/14 observations after the sixth day showed a red cell volume below the expected normal for the age of an order that would explain the fall in peripheral count). Although the red cell volume estimates during the first twenty-four hours after burning were often below the expected normal for the age, they were considerably higher than that found from the fourth day onwards. Comparison of total and transfused cell counts were made by differential agglutination tests with anti-M serum. The average finding was that transfused cells appeared to contribute to the loss of red cells to about the same degree as the patient's own cells.

During the first one or two weeks after a burn, when the fall in red cell volume appears to be the major cause of the burn anæmia, there were minor changes in blood films and reticulocyte counts. Hæmoglobin metabolism by the usual criteria was abnormal. The most dramatic change was a very variable erythrocyte protoporphyrin, which sometimes rose to two or more times the normal figure.

There have been many reviews of the causes of the anæmia of burns. That of Cope (1947) is perhaps the one which best expresses the current climate of opinions, and refers to the pioneer work in America which has emphasized the important role of fall in red cell volume affecting transfused as well as patient's cells (Moore *et al.*, 1946; Brooks *et al.*, 1951).

The present findings support the hypothesis that the major cause of the anæmia of burns before grafting is a disappearance of red cells. Although probably contributed to by the immediate effect of heat (Shen and Ham, 1943; Brown, 1946) and by hæmorrhage into exudate (Moore *et al.*, 1946) there remains a further unexplained loss of circulating cells that may prove to be the major cause of the anæmia and therefore appears worthy of further investigation. Although failure in the rate of red cell formation is probably one factor (Moore *et al.*, 1946; Cooray and De, 1949) even a complete failure could not explain the losses found.

The investigations by Miss S. Baar in this Unit suggest that the altered hæmoglobin metabolism as well as the unexplained disappearance of red cells is worthy of further investigation. The main finding is the raised erythrocyte protoporphyrin. The degree and acuteness of the changes suggests the possibility that more cells may be affected than could have matured during the time.

During the first two weeks after burning when red cell loss and abnormal hæmoglobin metabolism are most evident, there is also an enormous reticulo-endothelial response, with a very large outpouring of new leucocytes and other new cells to the burn area. There is, as also stressed by Cope (1947), some similarity between the anæmia of burns and the anæmia of acute infection. In both unexplained red cell disappearance involving a "curvilinear" disappearance of transfused red cells (Brown *et al.*, 1944) and an altered hæmoglobin metabolism (Cartwright *et al.*, 1946*a*, *b*; Grinstein *et al.*, 1948; Vaughan, 1948; James *et al.*, 1951) may be playing a part. To end with such a vague comparison stresses our ignorance of the mechansim of the fall in red cell volume in burns.

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Infection of Burns

Our knowledge of the bacteriology of burns is recent. Aldrich (1933) and Cruickshank (1935) isolated streptococci from burns, and such information was extended in the development of prophylaxis and chemotherapy (Colebrook *et al.*, 1944; Langohr *et al.*, 1947; Colebrook *et al.*, 1948). In superficial burns, it is doubtful whether healing is delayed by bacteria, but in burns with full-thickness skin loss they may cause obvious clinical infection, with prolonged inflammation, pain and delayed healing leading to severe contracture. Infection may spread locally and sometimes generally. Local infection may cause toxæmia.

Efforts to prevent these results have included early skin grafting, prophylaxis and therapy by antibiotics, aseptic dressing techniques, the use of air conditioning with filtered air for the dressing station, and other methods which have reduced but not eliminated infection (Colebrook *et al.*, 1948; Jackson *et al.*, 1951*a*, *b*; Lowbury, 1954).

Local pathogenic effects of bacteria.—Local infection is hard to recognize on a burn with much slough and exudate, but some assessment of the local pathogenic action of bacteria may be obtained from their interference with healing and skin grafting. As the presence of particular bacteria—even *Strep. pyogenes*—is not consistently associated with these effects, it is impossible to be certain whether, in a particular instance, delayed healing is the effect or cause of bacterial contamination.

A way of avoiding this difficulty is to suppress the growth of the organism in question by chemotherapy in approximately half of the burns and see whether these heal more quickly and take their grafts better than burns in which the organism is allowed to grow freely. For example, local polymyxin was found effective against *Ps. pyocyanea* and some coliform bacilli in a controlled prophylactic trial. Both grafting results and healing times were significantly better in those who had polymyxin, the average healing time of treated patients being three weeks shorter than that of the control patients (Jackson *et al.*, 1951*a*). We inferred that *Ps. pyocyanea* and other polymyxin-sensitive organisms were probably causing adverse local effects.

The local pathogenic action of *Strep. pyogenes* is more widely recognized than that of Gram-negative bacilli. It was confirmed in a comparison of graft failure (less than 80% take) in a series of patients whose burns were colonized by *Strep. pyogenes* at the time of operation (16/18—89%) and others in the same period whose burns had been cleared of *Strep. pyogenes* by oral Aureomycin (11/46—24%). Controlled trials of Aureomycin for *Staph. aureus* showed some evidence that staphylococci were also capable of preventing the take of skin grafts.

Evidence for the local pathogenic action of *Ps. pyocyanea* has come from another line of study. Pyocyanin was consistently shown to cause necrosis of human epithelial tissue culture at a concentration estimated from extraction of weighed gauze swabs to be exceeded in green exudate from some burns (Cruickshank and Lowbury, 1953).

General pathogenic effects of bacteria.—Aldrich (1933) put forward the hypothesis that infection plays an important part in the ætiology of shock. In the light of further studies, this view was rejected, but recent work (Fine, 1952) suggests that bacteria may cause shock to become irreversible. As treatment for shock improves, the role of bacteria in causing the pyrexia, wasting and occasionally death of badly burned patients who have survived the shock phase becomes of increasing clinical interest.

Cruickshank (1935) reported the isolation of *Strep. pyogenes* at post-mortem from the spleen of severely burned patients with the organism in their burns. In our experience of burned patients treated with antibiotics, blood culture has rarely been positive. The organism most commonly isolated from blood has been *Ps. pyocyanea*, which could sometimes be found in lesions of lungs, pleura and skin at post-mortem. An occasional source of septicæmia or pyæmia in the severely burned patient is septic thrombophlebitis starting in a vein used for administration of blood or plasma.

When the blood culture is negative, circulating toxins may be the cause of general symptoms. Attempts to demonstrate such a toxin in burned animals have given inconclusive results (e.g. Robertson and Boyd, 1923; Underhill and Kapsinow, 1931; Blalock, 1934). The appearance of antibodies produced in response to colonization by *Ps. pyocyanea* in burns (Fox and Lowbury, 1953) may result from the absorption of products of these bacteria. But the respective roles of tissue breakdown products and of bacterial toxins have not been defined, and further study on this problem is needed.

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