THE ENHANCEMENT OF INFECTION DURING SHOCK PRODUCED BY BACTERIAL TOXINS AND OTHER AGENTS.

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In a study of dermal infection in the guinea-pig by staphylococci and clostridia we demonstrated that simultaneously injected adrenaline temporarily diminished the supply of blood, and therefore of phagocytes, to the infective lesion (Evans, Miles and Niven, 1948), and suggested that the associated enhancement of infection was a consequence of this local inhibition of diapedesis. A similar inhibition of diapedesis in lesions induced by tubercle bacilli and staphylococci was observed by Delaunay and Pages (1945) in guinea-pigs severely intoxicated by the endotoxin of *Salm. typhi*. Delaunay, Lebrun and Cotereau (1947) later pointed out the resemblance of the acute intoxication to traumatic shock. These observations suggested to us an exploration in experimental shock of the relation of inhibition of diapedesis and the enhancement of infection, already indicated by our work on adrenaline.

MATERIALS AND METHODS.

Strains of bacteria.

Staph. aureus 21, a strain from Professor Wilson Smith producing no α-toxin, but coagulase-positive with guinea-pig plasma; *Cl. welchii* SR9; *Ps. pyocyanea* Scudder; *Proteus vulgaris* PR3, a wound pathogen; and *Bact. coli* 88. These strains were used by Evans, Miles and Niven (1948) in their tests with adrenaline. The cells from 24-hour cultures were washed once and resuspended in buffered saline or peptone water; 0·1 ml. of various dilutions were used for intradermal injection. Viable counts were made of the suspensions by the method of Miles and Misra (1938).

Shocking agents.

Crude endotoxins from faecal strains of *Bact. coli* and from *Pr. vulgaris* PR1 were made by differential ethanol precipitation of tryptic digests of acetone-extracted bacterial cells (Raistrick and Topley, 1934). The O somatic antigen of *Sh. shigae* was supplied by Dr. W. T. J. Morgan. The α-toxins of *Staph. aureus* and *Cl. welchii* were dried preparations of material precipitated by $(NH_4)_2SO_4$ from toxic culture filtrates, and dissolved as required. The preparations of magnesium adenosine triphosphate (MgATP) were supplied by Professor H. N. Green. For dehydration shock, 60 per cent (w/v) glucose in distilled water, sterilized by steaming, was injected intraperitoneally.

Stock albino guinea-pigs 280 to 500 g. in weight were used, depilated when necessary by a barium sulphide paste 18 to 24 hours before the experiment.

Intradermal injections were made into the dorsal half of the skin in the thoracic and lumbar region. In the tables and figures the lesion diameters are $\sqrt{Dd}$, where D and d are the major and minor diameters, except for very irregular or elongated lesions, of which the area was measured directly and $1{\cdot}13\times$ the square root of this value used. " Inflammation " (I) means marked hyperaemia and induration ; and " necrosis " (N) refers to the area of brown, yellow or grossly haemorrhagic skin, destined, as the lesion aged, to become either scabbed or ulcerated. The inflammatory diameters measured include the central necrotic areas.

The methods of estimating arterial pressures and capillary resistance are described in the appropriate sections.

For histological examination, the skin bearing the lesions was excised, tied without stretching to perspex supports, epithelial side upwards, fixed for 2 hours in corrosive sublimate containing 4 per cent acetic acid, removed from the support and tied again for a further 4 hours with the subcutaneous tissue upwards. It was then transferred to corrosive sublimate alone overnight, and after trimming, the specimen was fixed for a further six hours in corrosive sublimate alone.

EXPERIMENTAL.

The Effect of Shock on Staph. aureus *Skin Infection.*

Shock induced by bacterial endotoxins.

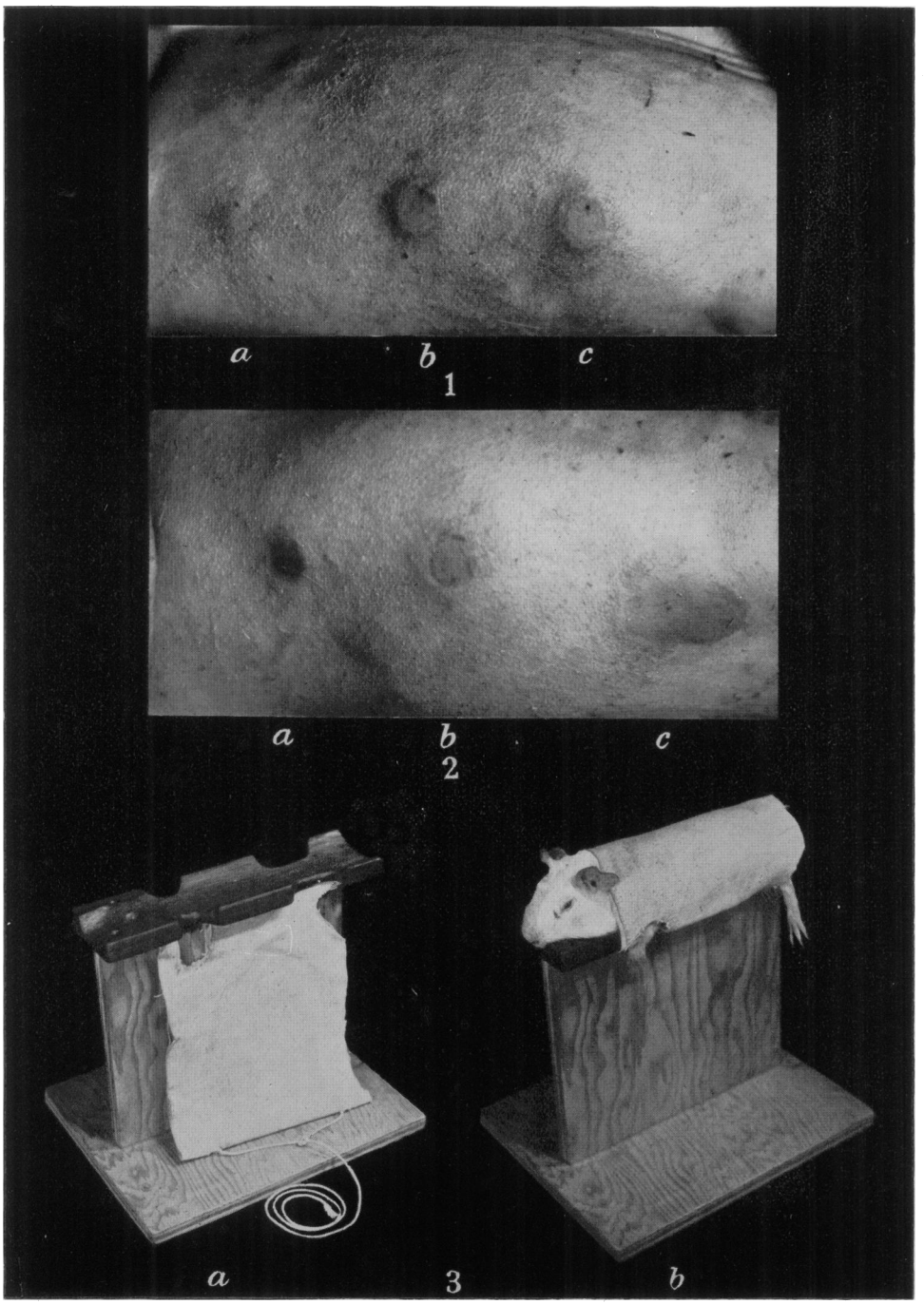
Though *Bact. coli* endotoxin (" colitoxin ") was used in most of the experiments, the shock induced and its effect on infection was indistinguishable from that induced by the endotoxins of *Pr. vulgaris* and *Sh. shigae* ; and the three may be considered together.

In skin lesions due to dead staphylococci, as Delaunay and Pages (1945) record, the leucocytic reaction was absent. Compared with unshocked animals, the absence was marked in sections of 2-hour-old lesions sampled at the height of shock, and evident in 24-hour-old lesions, when the animals had recovered from a shock lasting 3 to 8 hours. With living staphylococci, 24-hour-old lesions were strikingly different (Fig. 1*c* and 2*c*) ; for example, in a control animal, they were moderately inflamed and indurated nodules of 5 mm. in diameter, whereas in a shocked animal the same dose of cocci produced a lesion 17 mm. in diameter, with a central area of necrosis of 14 mm. The enhancement depends on the dose of toxin, which in turn determines the severity and duration of shock. In the example in Table I, central necrosis is small and the zone of peripheral inflammation is wide with the smaller doses of toxin ; but when the shock lasts 8 to 12 hours, necrosis is extensive and the inflammatory zone is narrow. That is, the longer the shock the smaller the inflammatory reaction during the succeeding hours.

EXPLANATION OF PLATE.

FIG. 1 and 2.—Active and retroactive enhancement of *Staph. aureus* skin lesions by colitoxin shock. Fig. 1, about 5 million living cocci injected ; Fig. 2, about 50 million. Photographed after 24 hours. (*a*) No retroaction ; lesion 3 hours old when colitoxin was injected. (*b*) Marked retroaction ; lesion ½ hour old when colitoxin was injected. (*c*) Direct enhancement ; lesion initiated during severe shock, three hours after injection of colitoxin.

FIG. 3.—(*a*) Stand for immobilizing guinea-pigs during blood-pressure determination on the ear. (*b*) Guinea-pig mounted on the stand.



Miles and Niven.

TABLE I.—*The Diameter of 24-hour-old Skin Lesions in Guinea-pigs Injected Intradermally with Graded Doses of* Staph. aureus, *2 hours after Intraperitoneal Injection of* Bact. coli *Endotoxin.*

Dose of living cocci.	Lesion-diameter (mm.). Guinea-pig and dose of toxin in mg.							
	1. 0·00.		2. 0·55.		3. 1·67.		4. 5·00.	
	I.	N.	I.	N.	I.	N.	I.	N.
$4·5\times10^{6}$	11	3	12	6	24	19·5	20	14
$4·5\times10^{5}$	5·5	—	8	3	16·5	14	20	11
$4·5\times10^{4}$	4·5	—	4·5	—	6·5	4·5	8·5	5·5
$4·5\times10^{3}$	3	—	3	—	7	4	5	3·5
$4·5\times10^{2}$	3	—	3	—	5	—	5	—

I = Inflamed area. N = Necrotic area.

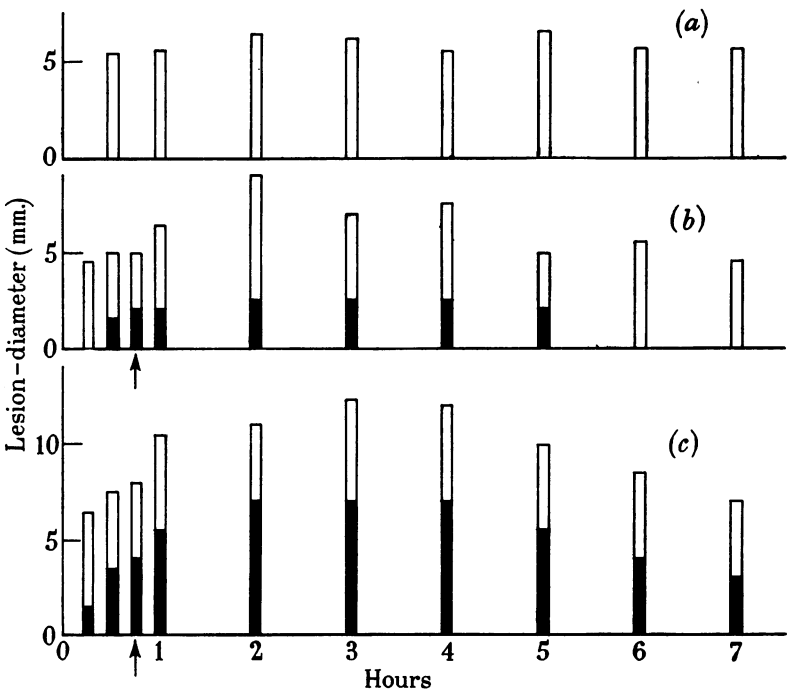


FIG. 4.—The enhancement in three guinea-pigs of lesions due to *Staph. aureus* injected before and during intoxication by intraperitoneal colitoxin. The height of the white and black columns indicate respectively the diameters of the inflamed and necrotic areas. The arrows indicate the injection of toxin. (*a*) No toxin ; (*b*) 1·25 mg. toxin ; (*c*) 5·00 mg. toxin.

As in all the experiments with *Staph. aureus* 21, about 5×10^{6} living cocci were injected, being the dose that in the unshocked animal produced an indurated, inflamed lesion 4 to 7 mm. in diameter without central necrosis (Fig. 1*a*).

The time relations of shock and enhancement are exemplified in Fig. 4 and 5, which record the results of typical experiments. Cocci were injected at intervals of an hour or less, and the colitoxin given intraperitoneally (Fig. 4) after the first

30 minutes; the lesions in unshocked animals have the same diameter and severity, proving that the suspension of cocci, held at 2° C. in 0·1 per cent peptone water, retained its infectivity throughout. With 1·25 mg. of the colitoxin, the

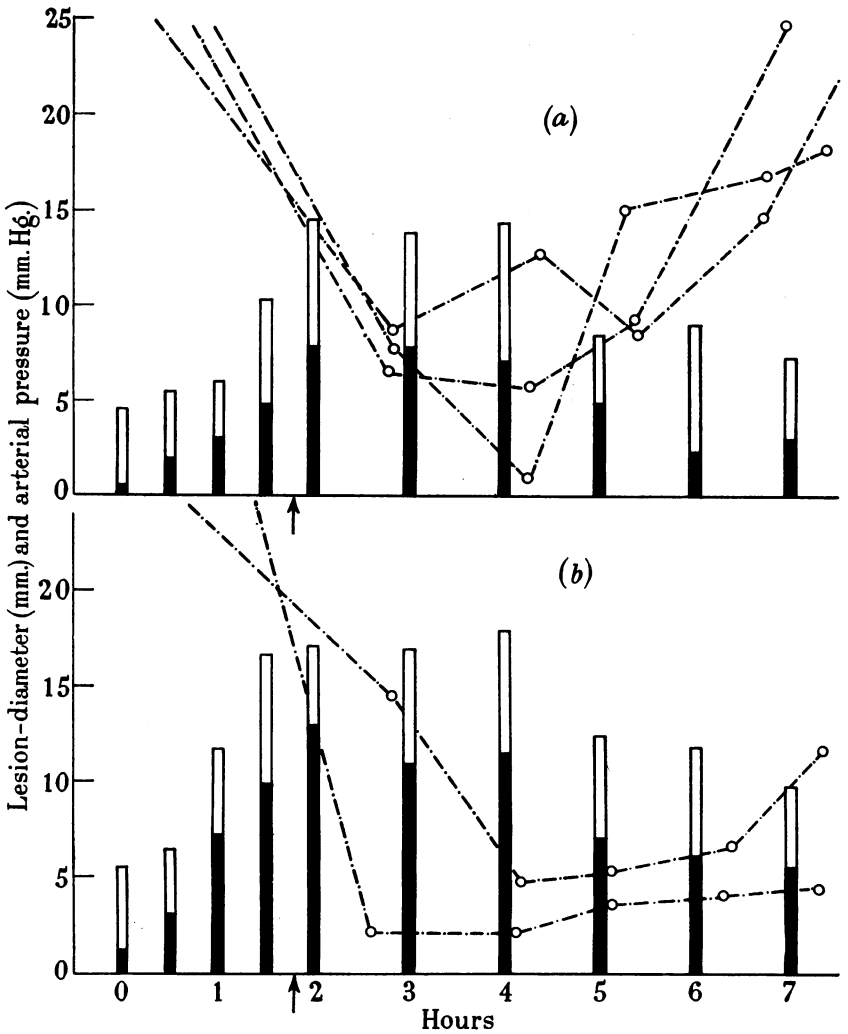


FIG. 5.—The enhancement of lesions due to *Staph. aureus* injected before and during intoxication by intravenous colitoxin. The height of the white and black columns indicate respectively the diameters of the inflamed and necrotic areas. The arrows indicate the injection of toxin. (*a*) 5 mg. toxin. The diameters are means from three guinea-pigs. The arterial blood pressures are recorded separately. (*b*) 7 mg. toxin. The diameters are means from two guinea-pigs. The arterial blood pressures are recorded separately.

4 to 5 hours' shock and enhancement were coincident and cocci injected 2 hours after the animals' recovery were not affected; with 5 mg. enhancement was greater and again all lesions injected during the 7 hours of shock were enhanced.

Retroactivity of Endotoxin Shock.

One feature of Fig. 4 demands special consideration—namely, the enhancement of lesions produced by cocci injected *before* the toxin. The smaller dose of toxin enhanced lesions 15 minutes old, the larger dose lesions that were 30 minutes old at the time of its injection. If shock is responsible for enhancement, it is in this sense "retroactive." With intraperitoneal colitoxin, shock took from 1 to 1½ hours to develop fully. By giving large doses of toxin intravenously (Fig. 5), severe shock was induced within 20 to 30 minutes, and in these instances, staphylococcal lesions already two hours old were enhanced (Fig. 5). In general, the older the lesion and the less severe the shock, the less the retroactitivy. But in none of 16 tests of various shocking agents was it possible to increase the retroactivity of the shock on *Staph. aureus* in the doses used, by more than two hours.

Allowing one hour for the maximum development of the shock, it is clear that in three hours the staphylococcal lesion is fully determined (Fig. 1 and 2); and after this lapse of time the induction of the profoundest shock short of death did not in our hands produce lesions that differed from those in control animals.

The histology of lesions modified by shock.

The progress of the staphylococcal skin lesions was determined by injecting a fixed dose of cocci at intervals, and excising all the injection sites after a given interval; the same animal thus yielded a series of lesions, e.g. 5, 3, 2, 1, ½ and 0 hours old. Shock was induced by colitoxin or hypertonic glucose, in some animals 5 hours, in some 3 hours, and in some 1 hour before the animal was killed and the lesions were excised. Fig. 6 summarizes the characteristic modifications in the tissue leucocytosis and fibrinous exudation in an experiment on four guinea-pigs. In the unshocked animal (Series 1) there was, with increasing age of lesion, a rapid and progressive increase in leucocytosis and exudation, without any noticeable increase in the number of stainable cocci originally injected. Series 2, 3 and 4 illustrate both the action and the retroaction of shock. In Series 2, the leucocytosis was diminished in the 3-hour lesion subjected to shock during the last hour, and suppressed in the ½-hour lesion that was initiated during shock. In Series 3 there was great diminution in the 5-hour lesion subjected to shock during its last 3 hours, and suppression in 3-, 1- and ½-hour lesions made during shock. The picture is similar in Series 4, except that the shock was passing off during the fifth hour, and some leucocytosis had occurred in the ½-hour lesion. In Series 2 and 3, and in the older lesions of Series 4, the number of cocci and the degree of tissue damage increased with the age of the lesion. There was also control necrosis, and at its periphery the capillaries were dilated, and the arterioles contracted, in the 3- and 5-hour lesions of Series 3 and 4.

The abundance of the tissue leucocytosis, therefore, is inversely related to the degree of enhancement exhibited by these lesions when they are allowed to mature for 24 hours in the living animal; and retroactivity in enhancement of infection is paralleled by retroactive diminution of tissue leucocytosis.

The vertical black columns in Fig. 6 represent the number of *healthy* phagocytes, but in shocked animals at least they do not represent the whole leucocytic picture. In all lesions that had been allowed to develop normally before the injection of the shocking agent there were numbers of degenerate polynuclear cells, the

degeneration ranging from mild nuclear and cytoplasmic changes, through pyknotic cells, to masses of karyolytic remnants of nuclei in the tissue spaces of the lesion. The longer the subsequent shock, the greater the degeneration of the phagocytes that had migrated into the tissues before the shock. Either the shock was in some way responsible for the acute degeneration of these leucocytes, or the abundance of healthy polynuclear cells seen in sections of the corresponding lesions in unshocked animals represents an equilibrium state in a continuous invasion of the tissues by blood leucocytes, which replace those whose

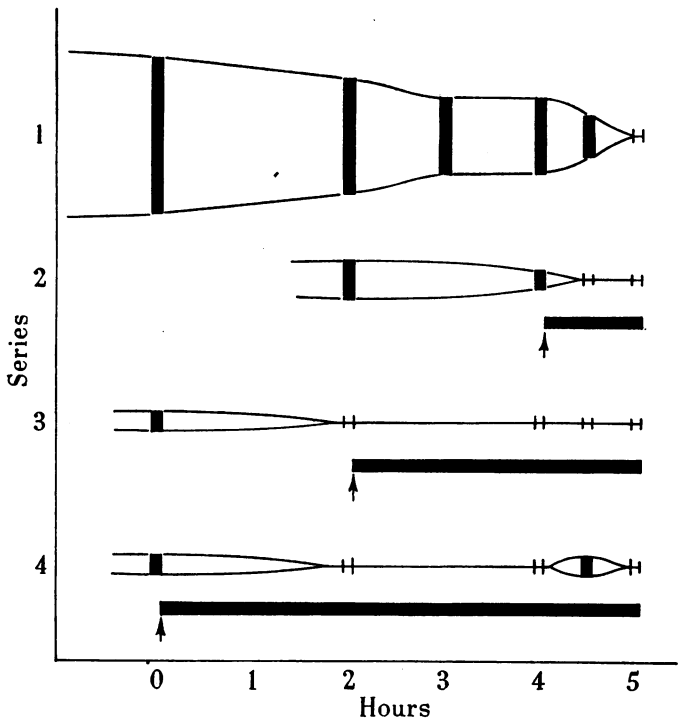


FIG. 6.—Tissue leucocytosis in response to intradermal *Staph. aureus* in normal and shocked guinea-pigs. The heavy vertical lines symbolize the relative amount of healthy phagocytes and fibrinous exudate in lesions initiated at the indicated hours and excised at the fifth hour. The arrow indicates the injection of the shocking agent, and the heavy horizontal lines the duration of the shock.

rapid destruction is a normal feature of the tissue reaction in the early stages of infection. The point is of considerable importance in determining the mechanism of enhancement of infection by shock (see discussion).

Shock induced by bacterial exotoxins.

The bacterial endotoxins induced prolonged shock without killing the guinea-pigs. It was more difficult to demonstrate great enhancement by exotoxins because shocking doses were close to lethal doses, and shock took longer to develop. Nevertheless, the enhancement of skin lesions, its time relation to the period of shock, and its rough proportionality to the severity of shock, were in

essence the same with the preparations of crude α-toxins of *Cl. welchii* and *Staph. aureus* given intraperitoneally. The possibility of a specific aggression action of the staphylococcal toxin on the *Staph. aureus* infection cannot be excluded, but at least it was not due to the α-toxin in the preparation used, since Strain 12 did not produce α-toxin.

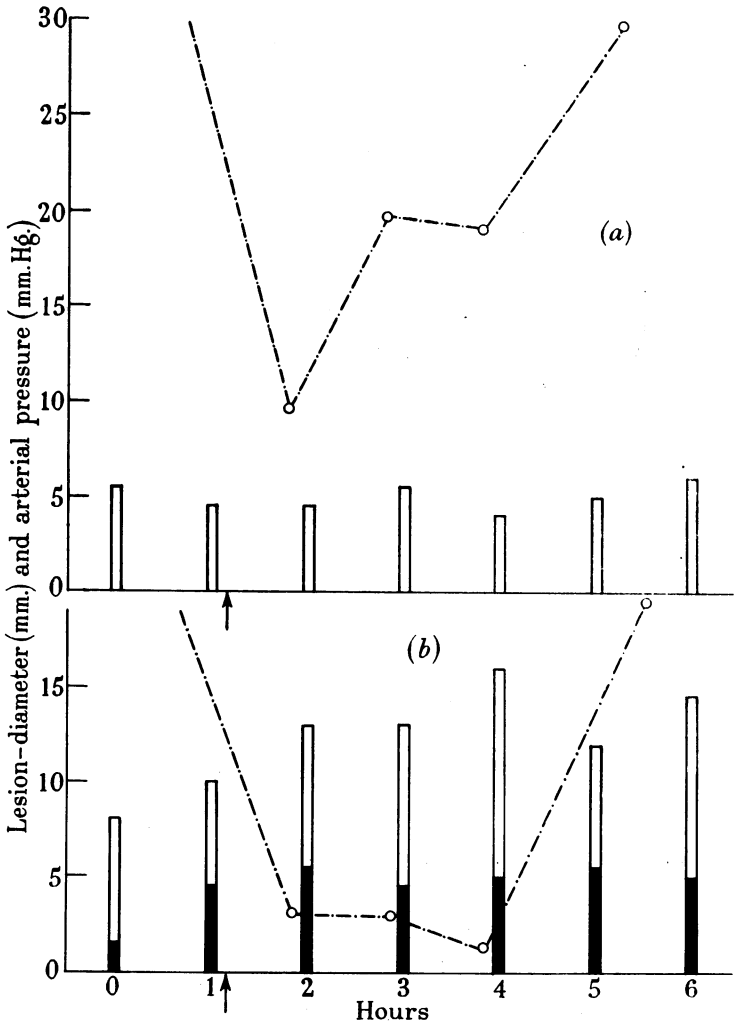


FIG. 7.—The enhancement of lesions due to *Staph. aureus* injected before and during intoxication by intraperitoneal magnesium adenosine triphosphate. The height of the white and black columns indicate respectively the diameter of inflamed and necrotic areas. The arrows indicate the injection of ATP. (*a*) Guinea-pig given 420 mg. ATP/kg. Arterial pressure does not drop below critical level; no enhancement. (*b*) Guinea-pig given 320 mg. ATP/kg. Arterial pressure reaches and remains for 3 hours below critical level; enhancement.

Shock induced by adenosine triphosphate and hypertonic glucose.

Severe but non-fatal shock was produced by 400 to 550 mg. of Professor Green's preparation of MgATP per kg. body weight, and dehydration shock lasting 2 to 6 hours by 15 to 20 ml. 60 per cent glucose per kg. body weight, though 20 ml. per kg. usually proved to be about LD50 for the stock guinea-pigs used. Both substances were given intraperitoneally. Here again (Fig. 7 and 8) the association of severity of shock, and enhancement of infection and degree of retroactivity, was essentially the same as with endotoxin shock.

None of the shocking substances tested modified the coccal lesions unless they were given in doses that induced recognizable shock.

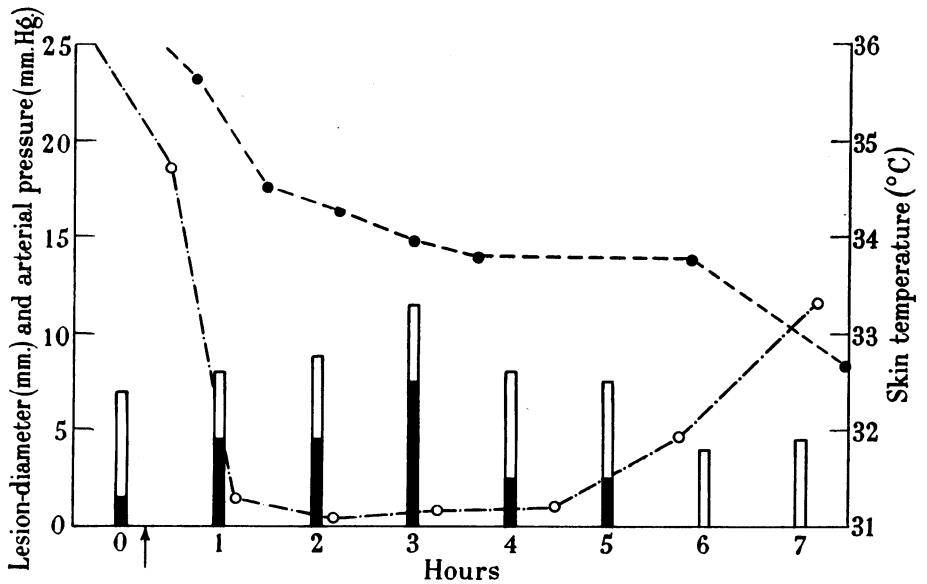


FIG. 8.—The enhancement of lesions due to *Staph. aureus* injected before and during intoxication by intraperitoneal hypertonic glucose solution. The height of the white and black columns respectively indicate the diameters of inflamed and necrotic areas; the open circles, arterial pressures; and the solid circles, skin temperature. The arrow indicates the injection of the glucose.

The Mechanism of Enhancement of Staph. aureus *Infections by Shock.*

After one to two hours' shock, the most striking departure from the norm of inflammation in lesions that later will prove to have been enhanced is the obvious absence of signs of inflammation in the infected skin, and histologically, the absence of phagocytes and a diminution of fluid exudate in the tissues. By analogy with the adrenaline ischaemia (Evans, Miles and Niven, 1948), it is possible that in shock also a local diminution in blood flow is responsible for the absence of leucocytes, and consequently for the relatively unimpeded growth and spread of staphylococci. Pickrell (1938) found that the enhancement of pneumococcal skin infections in the rabbit by ethanol intoxication was associated with absence of local leucocytic immigration, but that it was not due to a depression of phagocytic activity. He suggested that there were no leucocytes in the

infected tissues because the capillaries failed to respond to the injected pneumococci by dilation and increase in permeability.

Delaunay and his colleagues have worked extensively at this problem. Besides inhibition of diapedesis, they found in endotoxin shock that the carotid blood pressure was maintained at a high level until just before the death of the animal (Boquet, Delaunay, Lehoult and Lebrun, 1947). However, in the first 30 minutes of intoxication the skin of the animal became cold and pale, and scarcely bled on cutting (Boquet, 1942), peripheral circulation was diminished and 30 to 40 per cent of leucocytes disappeared from the peripheral circulation (Boquet, Delaunay, Lebrun and Lehoult, 1947*a*). At the same time, the circulation in the vascular beds of both skin and mesentery at first accelerated ; then arteries and to some extent veins underwent transient segmental contraction, followed by dilatation, when the blood flowed more slowly (Delaunay, Lebrun and Delaunay, 1947). The contractions and dilatations alternated until, just before death of a fully shocked animal, dilatation supervened. In the mouse and guinea-pig mesentery the circulation did not cease until just before death. The sequence was similar in the rabbit's ear (Delaunay, Boquet, Lebrun, Lehoult and Delaunay, 1948), but although temporary reversal of flow was observed in some capillaries and venules, there was never a true stagnation of the blood.

The term " inhibition of diapedesis " is question-begging if the meaning of " diapedesis " is properly confined to actual passage of leucocytes through the capillary walls. The absence of tissue leucocytes may be due to changes in the blood, the capillaries or the tissues, or to combinations of such changes, viz. :

(*a*) There may be so little blood flowing as to deprive the capillaries of the leucocytes necessary for diapedesis ;

(*b*) the blood, though flowing, may contain too few leucocytes ;

(*c*) a certain intracapillary pressure necessary to force the leucocytes through the endothelium may be lacking ;

(*d*) the leucocytes may lose an intrinsic power of diapedesis ;

(*e*) the capillaries may become more resistant to the passage in one direction of leucocytes, or of chemiotactic substances in the other ; and finally

(*f*) the infected tissues may not elaborate chemiotactic substances.

Of these possibilities (*b*) seems to us to have been excluded by Boquet, Delaunay, Lebrun and Lehoult (1947*a*) because in the leucopenia of shock the number of circulating leucocytes, though reduced, was still several thousand per mm^3 ; (*d*) is not proven ; and (*f*) is unlikely. With regard to (*a*) and (*c*) there are obviously profound vascular disturbances, but their connection with inhibition of diapedesis is obscure. With regard to (*e*), Delaunay, Pages and Cotereau (1946) describe a great increase in capillary resistance in guinea-pigs treated with shocking and non-shocking doses of endotoxin. Our results are consistent with (*a*) and (*c*)—a combination of diminished blood flow and pressure in the peripheral vessels. We have found no good evidence (p. 86) for an increase in capillary resistance or indeed for the absence of the increase in capillary permeability that characterizes acute infective inflammation.

Peripheral Blood Pressure in Shock.

There is no need to establish contemporaneity of systemic hypotension and enhancement of infection in order to connect the two phenomena causally. As

we have established, shock is retroactive, so that a late systemic hypotension might determine earlier enhancement. Moreover, the carotid blood pressure in shock might be maintained longer at physiological levels than arterial pressures in the skin and other peripheral organs. The passage of blood cells through the true non-muscular capillaries is intermittent (Krogh, 1929; see also Chambers and Zweifach, 1946), and in the resting state of, e.g. the skin, the capillary blood flow is largely shunted directly from the smallest arterioles to the smallest venules through certain channels (the a–v channels of Chambers and Zweifach, 1940, 1944). In progressive shock induced by bleeding or trauma, after an initial reactive period the capillary flow decreases further; and in severe shock, it may cease in the skin, though it still continues in the mesentery (Chambers, Zweifach and Lowenstein, 1943; Zweifach, Chambers and Lowenstein, 1944).

TABLE II.—*The Diameter of 24-hour-old Skin Lesions in the Ear of Guinea-pigs not Shocked (Group A) and Shocked (Group B) with Colitoxin.*

Group.	Dose of living cocci.	Shock.	Lesion-diameters (mm.) in four guinea-pigs. I.	N.
A	25×10^6	+	8·5, 10, 12, 9	4, 3, 5, 5
B	25×10^6	—	7, 4, 4, 4	2, 1·5, 2, 1·5
A	25×10^5	+	7, 6, 5, 6	3, 2·5, 1·5, 1·5
B	25×10^5	—	3, 1·5, 1·0, 3	0, 0, 0, 1·5

I = Inflamed area. N = Necrotic area.

We measured peripheral blood pressures in the ear of the guinea-pig, thus avoiding operative or anaesthetic procedures that might modify the vascular state of the animal, and were able to make repeated observations on vessels which represented, more closely than the central arteries, the vessels of the skin where enhancement was taking place. The degree of correspondence between ear and skin is hard to estimate. The ear certainly has a greater vascularity, both blood and lymphatic, than the skin of the trunk, and larger doses of living staphylococci are needed to induce good experimental lesions. Nevertheless, both colitoxin and hypertonic glucose will enhance staphylococcal lesions in the ear. In a typical experiment, approximately 25 and 2·5 million living cocci were injected in 0·025 ml. volume into the dorsal skin of the right and left ears respectively of 8 guinea-pigs, about 8 mm. proximal to the midpoint of the lateral margin. Four (Group A) were severely shocked with glucose; four (Group B) were controls (Table II). In shocked animals, the smaller dose of cocci produced mean lesion-diameters of 6·1 mm. inflammation and 2·1 mm. necrosis; the corresponding figures in the controls were 1·4 and 0·4. For the purpose of the tests, then, the ear vessels may be considered representative of those in the skin.

Arterial pressures in the guinea-pig's ear.

Pressures were measured by a modification of the capsule of Grant and Rothschild (1934), consisting (Fig. 9) of capsule, an illuminating device and a ×4 lens of 30 mm. working distance for the observation of small vessels. The guinea-pigs were placed on a narrow wooden platform, grooved longitudinally to take the

body and the chin and notched along the two edges to allow the legs to depend (Fig. 3*a*), and held by a broad linen band, leaving the ears and snout free (Fig. 3*b*). After a few minutes' experience, most animals were quiet enough for repeated observations and their very occasional squirming did not raise the blood pressure significantly. The median arterial tree in the guinea-pig's ear usually branches fan-wise from near the base towards the highly vascularized area round the main marginal veins. One of the smaller branches, 0·08 to 0·12 mm. in diameter, with no offshoots for a length of 2–3 mm. was used for an estimation of the diastolic pressure of the contained blood.

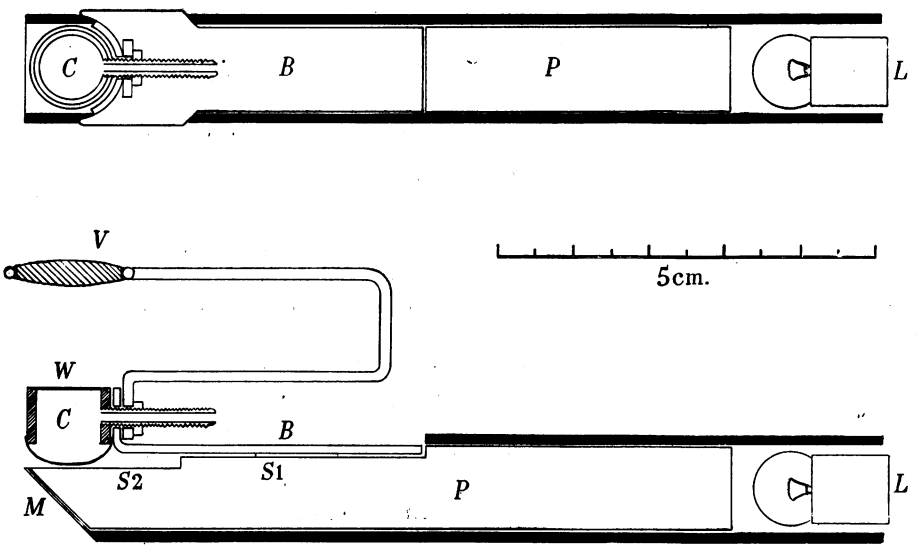


FIG. 9.—Modification of Grant and Rothschild's capsule, for measuring arterial pressure in the ear of guinea-pigs. C, capsule with diaphragm of gold-beater's skin, closed by a glass window, W. L, lamp (2 amp., 2 volt). M, mirror. P, Perspex total-reflection rod in bakelite sheath with a plane surfaces S_1 for the metal base (B) of the capsule-holder, and S_2, for supporting the ear during compression. V, viewing lens (×4) on adjustable soft wire support.

The animals were kept at laboratory temperature, and for each reading, vasodilatation of the arteries was induced by alternate compression (at 100 mm. Hg) and release, 5 to 6 times. In all but severely shocked animals, dilatation could be induced in this way, though the transient segmental contractions of the artery during the earlier stages of shock, noted by Delaunay *et al.* (1948), sometimes did not disappear until after more prolonged stimulation. The values for consecutive readings on vessels in this reactive state were reasonably steady—36, 38, 40, 40, 40, 38, and 6, 4, 8, 8, 6 mm. Hg are typical series at high and low pressures—and 4 to 5 readings were taken and averaged.

The pressures varied to some extent with the diameter of the vessel, and its distance from the base of the ear. But since only comparative readings of arterial pressures in skin were required, and not an indication of the systemic pressure, the variation could be ignored provided that the same piece of artery was used for each determination. The arterial pressure in normal animals lay

between 25 and 50 mm. Hg and in shock declined to <10 mm., 30 to 60 minutes after injection of the shocking agent. In severe shock the pressures were between 1 and 5 mm. Hg ; at these lowest levels the exact values were difficult to determine, even with a water manometer, owing to the insensitivity of the capsule ; but in these circumstances the pressures in the nearby veins of about twice the diameter, judging by their almost simultaneous filling as the capsule pressure was allowed to decline, were only a fraction of a millimetre Hg less than the arterial pressures.

Arterial pressures in inflamed ears.

Inflammation did not materially alter the arterial pressures in shocked animals, but in unshocked animals acute vasodilation of the artery under observation sometimes resulted in higher pressures. The arterial pattern in the middle of both ears of nine guinea-pigs was mapped, and arteries chosen, one in each ear, which gave similar pressure readings. Three animals were injected with an approximate LD50 of hypertonic glucose, and three with colitoxin. Half an hour later all received in one ear 0·03 ml. of a suspension of living *Staph. aureus* sufficient to give 7–10 mm. inflammatory induration in 24 hours. The suspension was injected intradermally over the test arteries and formed a bleb about 7–8 mm. in diameter. About 3 hours later, when all the intoxicated animals were acutely shocked and inflammation was obvious in the control ears, the arterial pressures were again measured (Table III). Only in two of the unshocked animals was there any marked excess of pressure on the inflamed side. In both control and test animals the vascular picture was greatly obscured in the inflamed area, only the larger vessels being visible, and these hazily ; and in the shocked animals the arterio-venous pressure differences were apparently less in the inflamed ear than in the opposite untreated ear. We may conclude that the behaviour of vessels in the untreated ear of shocked animals reflects that of skin vessels in areas infected by the staphylococci.

TABLE III.—*Arterial Blood Pressures Measured in Inflamed and Untreated Ears of Shocked and Normal Guinea-pigs.*

Guinea-pig.	Injection. For shock.	Injection. Into ear.	Arterial pressure (mm. Hg) in ear. Before the experiment.	Arterial pressure (mm. Hg) in ear. 3 hours after the injections.
1	Glucose	Staph.	38	?5
		Nil	42	6
2	,,	Staph.	42	?4
		Nil	40	4
3	,,	Staph.	44	20
		Nil	38	18
4	Colitoxin	Staph.	36	<6
		Nil	36	4
5	,,	Staph.	40	?4
		Nil	42	5
6	,,	Staph.	45	4
		Nil	40	5
7	*Nil*	Staph.	32	28
		Nil	28	28
8	,,	Staph.	36	46
		Nil	42	28
9	,,	Staph.	40	50
		Nil	40	34

The blood pressure in skin arteries during shock.

Fig. 5, 7 and 8 clearly show the association of enhancement and the levels to which arterial pressures drop in the ear. The greater and the more prolonged the drop, the greater both retroactive and direct enhancement (Fig. 5*a* and *b*). Susceptibility to ATP shock varied greatly in the guinea-pigs, and whereas a large dose that failed to lower the arterial pressure below 10 mm. Hg did not enhance infection (Fig. 7*a*), in another animal enhancement occurred with a smaller dose that lowered the pressure below this level (Fig. 7*b*). In none of the shocked animals was there any marked vasodilatation and this, in conjunction with the approximation of arterial and venous pressures observed in all severely shocked animals, suggests a greatly diminished flow of blood in the skin. The chilling of the skin in shock is consistent with this view. The cold skin, however, was not necessarily due to poor circulation. Temperatures were measured by

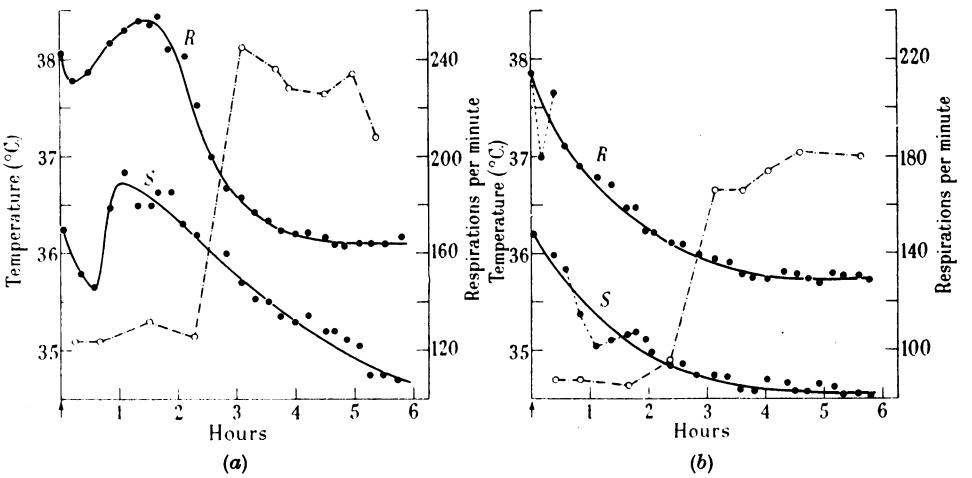


FIG. 10.—The rectal (R) and skin (S) temperatures (solid lines) and respirations (dotted lines) of guinea-pigs during shock. (*a*) Shock due to intraperitoneal colitoxin. (*b*) Shock due to intraperitoneal hypertonic glucose solution.

thermocouples applied to the skin of the thorax under two thicknesses of adhesive tape, or introduced into the gut, 4 cm. from the anus. In colitoxin and dehydration shock, both the skin and rectal temperatures were lowered ; and, except for an occasional transient hyperthermia with endotoxin preparations (Fig. 10*a*), a temporary drop in rectal temperatures after intraperitoneal glucose (Fig. 10*b*) and some fluctuations in the skin temperatures during the first hour, the time-temperature curves ran roughly parallel. This sequence was observed in both fatal and non-fatal shock. The cold skin therefore, may result from a good circulation of cold blood, and not a poor circulation of relatively warm blood.

The respiration rate increased when shock became severe (Fig. 10*a* and *b*). Its rapid increase was a useful index of the onset of shock.

In all our experiments with infection and shock, there was no enhancement unless, at some stage during intoxication, the arterial pressures in the ear dropped below 5–8 mm. and the arterio-venous pressure difference became small (*cf.*

Fig. 7*a* and 7*b*). Whether the absence of tissue leucocytes is directly due to a low capillary pressure, or to diminished blood flow, or both, must await microscopic studies *in vivo*, if possible of tissues in their natural state in unanaesthetized animals. Nevertheless, we feel that, with one exception, the facts elicited by Delaunay and his colleagues, and by ourselves, are compatible with the view that changes in the flow and pressure of the capillary blood are sufficient to account for the inhibition of tissue leucocytosis observed in shock.

The Demonstration of Capillary Resistance in the Guinea-pig.

The exception is the increase in capillary resistance after the injection of endotoxin reported by Delaunay, Pages and Cotereau (1946), who found that half an hour after shocking and subshocking doses of *Sa'm. typhi* endotoxin, the minimal suction of one minute's duration required to rupture the capillaries in the dorsal thoraco-lumbar skin had risen from 100–200 mm. to 600–650 mm. Hg. We have confirmed these figures in colitoxin, dehydration and MgATP shock. But we contend that in shocked animals the threshold pressures for rupture can vary independently of the resistance of the capillary walls.

Fig. 11*a* represents the hydrodynamic relation of blood vessels during cupping. A, a, c, v and V are respectively arteries, arterioles, capillaries, venules and veins, with manometers registering the appropriate pressures. The capillary pressure is p, and R the pressure under which the capillaries rupture. The *cuffing* method of measuring capillary resistance depends on the occlusion of the veins only. The pressure in c rises, and when R is reached, petechiae are produced; i.e. given similar arterial pressures, differences in the time taken to produce rupture will reflect differences in capillary resistance.

Ideally, the *cupping* method should be equivalent to applying a suction cup (C_1, Fig. 11*a*) to the top of the capillary manometer; i.e. there is never any occlusion of the vessels. In reality, a cup (C2) is placed over a wide area of skin. When the suction is less than local arterial pressures, veins only are occluded and the effect is the same as in cuffing. With suction pressures of 100–200 mm. Hg, all the vessels at the edge of the cup are occluded and the vascular network within becomes a closed bag of blood, which is ruptured when the atmospheric pressure transmitted through the tissues presses it against the tense dome of skin inside the cup (Fig. 11*b*). The amount of blood within the closed system will depend on the state of the vessels when the cup is applied. As the suction pressure rises, blood will be sucked in after the occlusion of the veins and before the occlusion of the ovaries. If it could be assumed that the vessels within the cup always filled to the same extent, then the pressure required to rupture the distended capillaries would be a function of the resistance of the capillary walls. On the other hand, if there were little blood in the skin and if the local arterial pressures were low, the vessels within the cup would be less distended and a much greater pressure required for their rupture (Fig. 11*c*); and an increased rupture-pressure would result solely from a decreased blood supply; as, e.g., in an ischaemic skin.

The correctness of this interpretation is borne out by the following observations.

Histology of the cupped areas of skin.—A standard suction of 250 mm. Hg was applied for 1 minute to the skin of normal and shocked guinea-pigs, using

a small cup of 11 mm. external, 7 mm. internal, diameter, and 9 mm. deep. The tested areas were immediately excised. In stained sections of sites bearing petechiae, the arterioles were almost empty, the venules partly empty, and the capillaries distended with blood; rupture had occurred mostly at the venous ends of the capillaries. In sites without macroscopic petechiae there was little blood in either arterioles or venules, the capillaries were less distended with blood, and only a few small haemorrhages were seen in the deeper parts of the

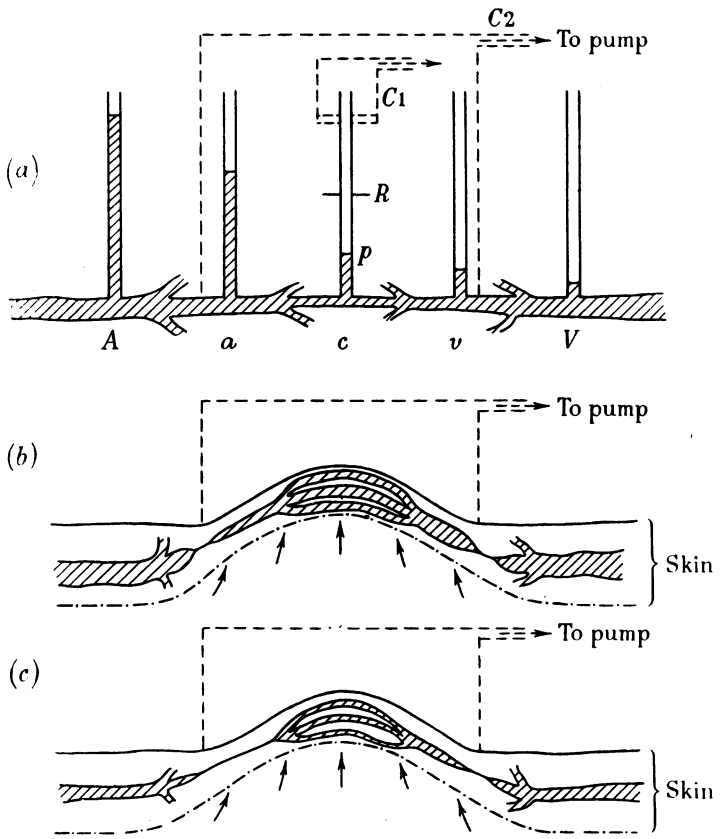


FIG. 11.—Diagrams of the hydrodynamic state of the blood vessels in the skin during cupping (p. 86). (*a*) C1 and C2, the ideal and actual position of the cup during the estimation of capillary resistance. (*b*) Distension of the capillaries in hyperaemic skin cupped at suction pressures over 100 mm. Hg. (*c*) Incomplete distension of the capillaries in ischaemic skin cupped at suction pressures over 100 mm. Hg.

skin, where the larger blood vessels lay. The various vessels were distended in the first place inversely as the thickness of their walls, and secondly in relation to the amount of blood trapped in the cupped area of skin. The distension of the vessels and the trapping of blood during the application of the cup was readily observed under a 20 × magnification with a 3 mm. glass cup placed on the trans-illuminated ear of an anaesthetized guinea-pig, by gradually applying a suction of 100 mm. Hg.

The relation of susceptibility to cupping and the distribution of skin vessels.—Susceptibility to cupping in the normal guinea-pig increases with proximity to underlying larger vessels, suggesting that nearness to an easily-sucked supply of blood is necessary for distension of the capillaries. This is clear from Fig. 12, exemplifying tests on several animals. A depilated guinea-pig was cupped at regularly spaced sites on one flank for 1 min. at 200 mm. Hg and immediately killed. The skin was incised over the spine, reflected ventrally, and the main skin vessels mapped in relation to the cupped areas. The skin of the lower belly was practically insusceptible. The most consistently susceptible area lay along a line parallel to, and 15–20 mm. from the lower thoracic and lumbar spinal midline, in close relation to the vessels that emerge from the body musculature. Susceptibility was less, though marked over the sacrum, but even along

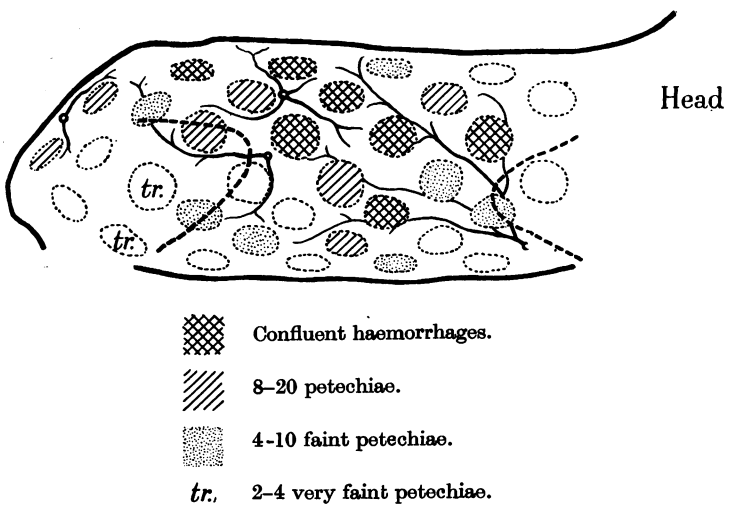


FIG. 12.—Variation of the susceptibility to capillary rupture by cupping, in relation to the branches of the main blood vessels underlying the skin of a 300 g. guinea-pig's right flank. A suction of 200 mm. Hg was applied for 1 minute to each marked area.

this line it was not uniform. Over twenty guinea-pigs were cupped in various ways and all had susceptible areas similar to those in Fig. 12. But even in such areas it was impossible to depend on any constant uniformity of response; confluent petechiae might appear in one site and none in the site immediately adjacent to it. But in nearly all the instances examined by dissection these close topographical differences were related to the position of the larger vessels on the undersurface of the skin.

For cupping tests even in the normal animal, areas of comparable susceptibility must be tested; and many sites in each animal, must be tested to allow for topographical variation. In the same animal the susceptibility was usually symmetrical about the spinal midline; and for the following tests, a line of cupped sites was first established as a control along one side of the spine of the depilated animal, and the exactly corresponding sites on the other side marked in readiness for the experiment. During marking the animal was made to sit

quietly with the spine in a straight antero-posterior line, and all distortion of the mobile skin by handling was carefully avoided.

The effect of blood supply on susceptibility to cupping.—Tested by the method outlined in the preceding paragraph, animals in a state of shock, with blood pressures of 10 mm. or less in the arteries of the ear, required cupping for 1–2 min. at 600 mm. Hg to produce petechiae similar to those made in the normal animal at 200 mm. Hg. Freshly killed animals are almost insusceptible to cupping at 600 mm. Hg. Guinea-pigs under urethane anaesthesia are susceptible, but if gradually bled dry from the carotid, become less susceptible. A simple and convincing proof of the relation consists of anaesthetizing guinea-pigs with chloroform or A.C.E. (alcohol, 1 vol., chloroform 2 vol., and ether 3 vol.); and over five-minute periods alternating a cyanotic, almost moribund state of deep anaesthesia with a light second stage. The skin susceptibility changed from almost insusceptible to normal susceptibility, and at the same time the arterial pressures in the ear alternated between 3 to 10 mm., and 20–40 mm. Hg (Table IV).

TABLE IV.—*Petechiae produced by cupping the skin of guinea-pigs for* 1 *minute at* 200 *mm. Hg., during alternating deep and light anaesthesia, compared with control sites cupped before anaesthesia.*

	Cupping.			
	Initial.		During anaesthesia.	
	Arterial pressure in ear (mm. Hg).	Petechiae* in control sites.	Petechiae in contralateral test sites.	Arterial pressure in ear. (mm. Hg).
Guinea-pig 1	28	7++	2±	10
		15++	10+	22
		C	3±	10→3**
		C	C	24
		6+	*Nil*	10→4**
		C	C	20
		8+	*Nil*	10→3**
		15+++	,,	12
		C	C	25
Guinea-pig 2	40	18+	*Nil*	4
		7+	1+	12
		10++	2±	10
		8++	*Nil*	8→4**
		C	8+	6
		1+	*Nil*	7
		C++	,,	10

* The figures indicate the number of petechiae, and ±, +, ++, +++, increasing grades in size of petechiae and intensity of colour. C = Confluent petechiae.

** Arterial pressures at beginning and end of cupping period.

By suitable adjustment of the anaesthesia, and using half-minute cupping periods, the change could be induced, and the animal allowed to revert to the normal state, within one minute. Serial sections of the resulting lesions also demonstrated the importance of well and readily filled vessels for rupture in the cup; because, although no petechiae were visible on the surface of sites cupped during the moribund state, there were a few on the underside of the skin, and these proved to result almost entirely from arteriolar, not capillary rupture. The rapid

induction and the ready reversion of the anaesthetic effect excludes the probability of a direct modification of the resistance of the capillary walls ; and the theoretical, and the other experimental considerations give no indication that anything other than variation in blood content is needed to explain the apparent change in peripheral capillary resistance during shock. We have, nevertheless, no direct proof that resistance does not rise during endotoxin shock, but we submit that there is no unequivocal evidence that it does.

We are, moreover, unable to confirm the observations of Delaunay, Pages and Cotereau (1946), that subshocking doses of endotoxin significantly increase the minimal rupturing suction. In our hands the susceptibility of guinea-pig skin to a standard suction was far too variable to allow any tests other than a semi-quantitative comparison of the degree of haemorrhage in a row of treated sites made before the intoxication, with that in the corresponding contralateral sites tested $\frac{1}{2}$, 1 and 2 hours after injection of the toxin. Only when arterial pressures in the ear were substantially lowered did the susceptibility to cupping diminish significantly. In any event, the increased capillary resistance reported with subshocking doses of toxin cannot be operative in the inhibition of diapedesis, because, as both we and Delaunay and Pages (1945) have shown, inhibition does not occur unless there is demonstrable shock.

The Effect of Blood Supply on Manifestations of Capillary Permeability.

Delaunay, Pages and Cotereau (1946) also record that the exudation of circulating trypan blue in response to substances (e.g. peptone) which increase capillary permeability, is inhibited in shock. As Landis (1946) points out, the rate of escape of dye into the tissues does not depend only on capillary permeability.

The following experiments show that transient mechanical interference with the blood supply of the skin can readily produce results similar to those following changes in capillary permeability.

1. The intradermal injection of 0·5 μg. histamine in 0·1 ml. into a normal guinea-pig with 75 mg. pontamine sky blue X per kg. body weight in its circulation, will regularly, within 2 to 3 minutes, produce a deep blue coloration of the skin 7 to 10 mm. in diameter. When the site of injection is immediately covered by a glass cup 20 mm. in diameter, and a suction of 40 to 60 mm. Hg applied to occlude the vessels at the edge of the cup, the blueing is inhibited as long as the cupping is maintained.

2. When a similar animal is mildly shocked, by colitoxin or dehydration, the blueing of the histamine lesion is retarded ; at most a pale blue spot 3 mm. in diameter appears after 10 to 15 minutes. But if the cup is applied to the injection site and a suction of 10 to 12 mm. Hg applied for 2 to 3 seconds every 10 seconds so as to promote the flow of exudate without continuously occluding the veins of the skin, substantial blueing of the histamine-treated area occurs within 5 minutes ; i.e. histamine, as in the unshocked animal, had induced an increase in the permeability of the vessels, but a diminution in blood supply had prevented its manifestation by the exudation of dye.

As an additional illustration of the dependence of cupping phenomena on a ready supply of blood, it should be noted that this manifestation of blueing by intermittent cupping, like the production of petechiae by cupping, was most readily elicited in the most vascular areas of the skin (*cf.* Fig. 12).

The Effect of Shock on Cl. welchii *and* Ps. pyocyanea *Skin Infection.*

Shock by colitoxin, hypertonic glucose and MgATP enhanced skin infection by *Cl. welchii* and *Ps. pyocyanea*, both directly and retroactively; and as with *Staph. aureus* infections, enhancement took place only with shock sufficient to lower the arterial pressure in the ear to 10 mm. Hg. Retroaction was more marked with *Ps. pyocyanea* than with *Cl. welchii*; *pyocyanea* lesions up to four hours old at the time of injecting the shocking agent were enhanced.

TABLE V.—*The Diameter of 24-hour-old Skin Lesions in Guinea-pigs injected Intradermally with Graded Doses of* Cl. welchii, *2 hours after Intraperitoneal Shocking Doses of Colitoxin.*

Guinea-pig.	Dose colitoxin (mg.).	Lesion-diameters (mm.) with *Cl. welchii*.					
		10^7.		10^6.		10^5.	
		I.	N.	I.	N.	I.	N.
1	7·5	25	13*	25	13*	20	17*
2	5·0	28	16*	19	12*	(4)	—
3	0·0	13	10*	(5)	—	(5)	—

I = Inflamed area, N = necrotic area.
* Lesions also spread ventrally with necrosis and oedema extending to midline.
The figures in brackets indicate slight inflammation.

A given dose of *Ps. pyocyanea*, like *Staph. aureus*, produced severe lesions with the more severe shock. *Cl. welchii* was affected rather differently; only severe shock enhanced infection by this microbe, and a given dose either was unaffected, producing a small, mildly inflamed swelling, or greatly enhanced into a large necrotic area with gravity extension down the flank and a sac of soft oedema in the anterior belly wall. The larger the dose of shocking agent, the smaller the dose of *Cl. welchii* that was enhanced in this " all or nothing " manner (Table V).

Histology of Cl. welchii *lesions.*—The histology of the *Cl. welchii* lesions was explored in the way described (p. 77) for the *Staph. aureus* lesions. The dose of *Cl. welchii* used was rather large, and in unshocked controls produced a severe lesion with necrotic centre in 24 hours. The tissue reaction during the first four hours differed from that with *Staph. aureus*. There was a progressive increase in the number of bacilli, and in collagenous degeneration and necrosis at the centre of the lesion. The lesion spread both laterally and vertically, until at four hours there was degeneration and necrosis of the superficial epithelium, and in the muscular layer immediately over the subcutaneous spaces. The necrosis affected the abundant polynuclear leucocytosis that had already taken place in half an hour, but there was, up to four hours (the oldest lesion studied), an increasingly active exudation of healthy phagocytes at the periphery of the necrotic area. In shock, the infection and necrosis spread more rapidly, and bubbles of gas appeared within one hour and were a striking feature of the older lesions, where enhancement in size was accompanied by a proportional increase both in gas and the number of clostridia; but, as with staphylococci, both fibrinous exudate and phagocytes were greatly diminished in retroactively affected lesions, and suppressed in actively affected lesions. Retroaction appeared to be much more severe than in staphylococcal lesions, presumably

because the already migrated leucocytes were more rapidly destroyed by *Cl. welchii* in the large dose used, than by the relatively small dose of *Staph. aureus*. As in the " shocked " staphylococcal lesions, the capillaries were dilated and the arterioles contracted at the periphery of the necrotic areas.

The Effect of Shock on Bact. coli *and* Pr. vulgaris *Skin Infection.*

We tested strains of two other bacteria, *Bact. coli* and *Pr. vulgaris*, which in our previous experiments had been enhanced by adrenaline. The result was surprising because the general picture was that of inhibition, not enhancement, of the infection by shock. Graded doses of the two strains were injected during

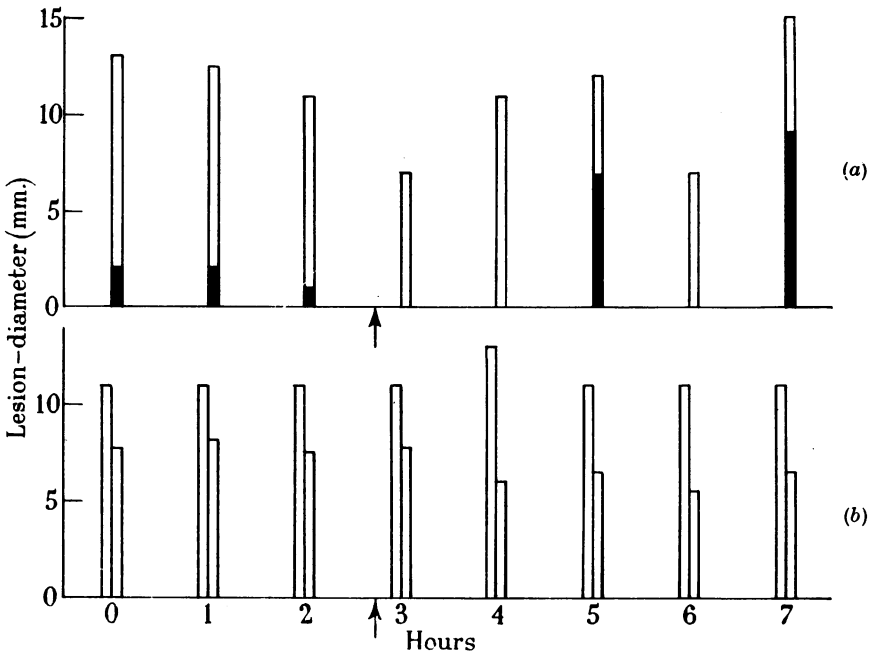


FIG. 13.—The effect of intoxication by colitoxin on lesions due to *Bact. coli* injected before and after the colitoxin. The height of the white and black columns respectively indicate the diameters of inflamed and necrotic areas. The arrows indicate the injection of the toxin. (*a*) Erratic enhancement of lesions made late in the shock. (*b*) Diminution of lesions. At each hour the left-hand columns represent lesions in one control animal, the right-hand columns the mean of lesions in two shocked animals.

the height of colitoxin shock, $2\frac{1}{2}$ hours after the injection of toxin ; and there was little doubt that the 24-hour lesions in the intoxicated animals were substantially smaller than those in unshocked animals (Table VI). At 24 hours the intoxicated animals had fully recovered from the colitoxin, and the infecting microbe could not be grown from the blood or the viscera. We were not therefore dealing with an absence of localized inflammatory reaction in persistently shocked or otherwise moribund animals. Nor was the result with *Bact. coli* likely to have been due to a specific effect of the colitoxin ; because the colitoxin was serologically distinct from the O antigen of the infecting strain ; and the antigenically unrelated *Pr. vulgaris* was similarly affected.

TABLE VI.—*The Diameter of 24-hour-old Lesions due to Graded Doses of* Pr. vulgaris *and* Bact. coli *in Guinea-pigs Shocked with Colitoxin 2 hours previously.*

Guinea-pig	Infecting microbe.	Dose of colitoxin (mg.).	Lesion-diameters* (mm.) with suspensions diluted.							
			10^{0}.		10^{-1}.		10^{-2}.		10^{-3}.	
			I.	N.	I.	N.	I.	N.	I.	N.
1	*Pr. vulgaris*	5·0	10	—	7	—	(4·5)	—	(2)	—
2	*Pr. vulgaris*	*Nil*	18	2	10·5	—	8·0	—	(5·5)	—
3	*Bact. coli*	7·5	9	3	—	—	—	—	—	—
4	*Bact. coli*	5·0	10·5	5	(4)	—	—	—	—	—
5	*Bact. coli*	*Nil*	19	4	12·5	—	8·5	—	(4)	—

I = Inflamed area ; N = necrotic area.

* The diameters are means of two lesions, on the right and left flanks of each animal. The figures in brackets indicate slight inflammation.

Not all *Bact. coli* lesions, however, were diminished in shock. As the experiments summarized in Fig. 13 show, although shock diminished all the lesions in two guinea-pigs (whose lesion-diameters are averaged in Fig. 13*b*), in a third animal the lesions made early in shock were diminished and those made late were enhanced. This phenomenon was observed on other occasions, though erratically. It is possible that the conditions necessary for enhancement by shock are much more critical for *Bact. coli*, and perhaps for *Pr. vulgaris*, than for *Staph. aureus*, *Cl. welchii* and *Ps. pyocyanea*. The phenomenon clearly needs investigation ; in the meantime it provides a useful check on too-ready generalizations about the nature of the enhancement in shock.

DISCUSSION.

We have demonstrated an association between enhancement of skin-infection and shock sufficient to lower the pressure in smaller arteries of the skin below a certain value ; the degree of enhancement is directly related to the suppression of leucocytosis in the infected tissues. Shocking agents differing as widely as colitoxin, *Cl. welchii* α-toxin, magnesium adenosine triphosphate, and intraperitoneal hypertonic glucose enhance according to the length of time they lower peripheral blood pressure. None of them appears to have a specific effect on the infection by *Staph. aureus* or *Cl. welchii*. Our results accord with those of Howie and Cruickshank (1947), who enhanced the lethal effect of anthrax spores in mice by the simultaneous injection, at a different site, of shocking doses of MgATP and hypertonic glucose. The relatively little enhancement observed may have been due to the spores' being injected intraperitoneally, for it is possible that in shock the vessels of the peritoneum retain their normal activity longer and to a greater degree than the vessels of the skin do.

In stressing diminished blood supply and low blood pressure as the immediate cause of a local failure of the defences against infection, we are aware that the analysis omits much that may be relevant, including humoral factors and physicochemical changes in the skin tissues. It seemed more profitable to begin with the immediate consequences of vascular change. There remains much to be settled. For example, is there in shock a complete stop in the supply to the capillaries of blood-borne leucocytes ? If the stoppage of circulation, as appears at present, is only partial, why are phagocytes not seen in the tissue sections ? For reasons given above, we are not inclined to admit the hypothesis of an increased resistance

of the capillary walls as an explanation. Moreover, our own observations provide an alternative. The absence of tissue leucocytes may be due, not to a complete suppression of diapedesis, but to a diminution in the number of leucocytes passing through the endothelium ; and if tissue leucocytosis at any moment is dynamic, in the sense that leucocytes are rapidly destroyed or removed, and as rapidly replaced from the blood, even a partial failure in replacement might soon lead to a virtual absence of leucocytes.

This explanation leaves inviolate the view that phagocytes go through the capillary endothelium under their own power. The view is generally held, but we know of no observation proving it. We do not know whether the intracellular forces behind the amoeboid movements of the polynuclear cells in relatively free conditions are sufficient to move a phagocyte through narrow holes in the capillary endothelium. It may well be that there is a critical intracapillary blood pressure required to help the leucocytes through the endothelium, either by a direct push, or by stretching the capillary wall so as to produce holes large enough for the passage of the leucocytes under their own power ; and that in shock the pressure remains for some time below this critical level. We are investigating these matters.

Our work on enhancement has so far been confined to pathogens that are neither natural infectors of the guinea-pig, nor, with the exception of *Cl. welchii*, capable in the doses used of spreading from the injection site and producing a widespread infection or toxaemia. It would therefore be unwise to speculate about the effect of shock on infection in general, especially in view of our observation that *Bact. coli* and *Pr. vulgaris* infections were sometimes *inhibited* by shock.

Nevertheless, we have established one feature of shock as an enhancer of *Staph. aureus* and *Cl. welchii* infection that deserves comment—namely, its limited retroactivity. Both *Staph. aureus* and *Cl. welchii* are common inhabitants of the immediate environment of men, and both, though especially *Staph. aureus* (see Williams and Miles, 1950) are likely to be driven into wounds at the time of their infliction. The development in the wounded man of severe traumatic shock is unlikely to inhibit the suppression of these two microbes by the naturally resistant tissues, unless it takes place within the first 2 to 3 hours after wounding ; because, if the argument from guinea-pig to man is valid, neither the coccal nor the clostridial lesion will be much modified by shock after this interval. The rarity of acute infection in traumatic shock, provided that no masses of ischaemic or dead tissue are left in the wound, probably reflects the rapidity with which the decisive tissue defences are normally mobilized.

In the guinea-pig these three-hour lesions are also insusceptible to local adrenaline (Evans, Miles and Niven, 1947). It appears that the decisive reactions both of the bacterium and the host tissues are displayed in the first three hours of infection, and determine within narrow limits the subsequent course and outcome of the disease. If this is so, the exploration of the defences against infection, as distinct from defences against the consequences of infection when it is once established, should be directed particularly to this short initial period.

SUMMARY.

Skin infections by *Staph. aureus*, *Ps. pyocyanea* and *Cl. welchii* were enhanced when guinea-pigs were shocked within 2 to 3 hours of the intradermal injection

of the bacteria. Older lesions were not affected, even by severe shock, suggesting that the outcome of these infections in the guinea-pig, is fully determined in 2 to 3 hours. *Bact. coli* infections were sometimes enhanced, sometimes diminished by shock ; *Pr. vulgaris* infections were diminished.

Enhancement was independent of the shocking agents used—bacterial endotoxins and exotoxins, magnesium adenosine triphosphate and intraperitoneal hypertonic glucose—and was associated with the absence of observable leucocytes in the infected tissue. It was produced only by shock sufficient to bring the peripheral blood pressure below the critical level represented by a pressure of less than 10 mm. of mercury in the small arteries of the ear ; and to maintain it at the low level for an hour or more.

The absence of tissue leucocytes is probably due to a diminution in the flow and the pressure of blood in the capillaries of the infected skin, resulting in a gross diminution of the supply of blood-borne leucocytes to the lesion. There was no evidence in the shocked guinea-pig of an increase in the resistance of the capillary walls to diapedesis of leucocytes.

The cupping method of measuring capillary resistance is inapplicable to shocked animals.

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