THE RELATIONSHIP BETWEEN THE VASCULAR MANIFESTATIONS OF SHOCK PRODUCED BY ENDOTOXIN, TRAUMA, AND HEMORRHAGE

II. The Possible Role of the Reticulo-Endothelial System in Resistance to Each Type of Shock*

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Comparative studies of the vascular reactions to bacterial endotoxins (1) and those following hemorrhage or trauma (2) have led us to suspect that the reticulo-endothelial system (RES)[1] may be an important determinant of the vasculotoxic manifestations of these syndromes. Two avenues of approach have in the main been used to define the physiological potentialities of this ubiquitous system. It is possible to measure what has been regarded as the principal functional attribute of the RES, its phagocytic capacity, by the rate at which standard amounts of a suitable colloid, such as carbon or chromium phosphate, are cleared from the blood stream (3, 4). In addition, use has been made of the fact that the phagocytic function of the RES can be predictably altered either in the direction of decreased activity by administration of a single large dose of colloid, or by suitably spaced, repeated doses of colloid (5) to provide an increased or stimulated phagocytic capacity.

These methods are not completely satisfactory, since there are no direct means of establishing whether the changes, which develop concomitantly in other phenomena, are actually the result of an altered status of the RES elements *per se*. They do, however, possess the merit of providing a direct and comparatively simple means of influencing this otherwise inaccessible system and thereby making it amenable to experimental study.

Various colloidal materials, known to be taken up by the reticulo-endothelial phagocyte cells, were therefore injected as a means of investigating the validity

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[1]RES, reticulo-endothelial system.

of the assumed interrelationship between the RES, bacterial endotoxins, and the behavior of the peripheral vascular bed during hemorrhagic and traumatic shock. It seemed reasonable to assume that if an interlocking of the two factors existed, conditions which interfered with the phagocytic function of the RES should lead to one pattern of response, whereas agencies which stimulated phagocytosis should have an effect in the opposite direction. Both of these possibilities were therefore explored.

The data reaffirmed the basic identity of the shock reactions produced by bacterial endotoxins, hemorrhage, or trauma, since they were influenced in a similar manner by changes in the phagocytic function of the RES. "Blockade" predisposed to the development of the vasoinhibitory reactions characteristic of irreversible shock, whereas "stimulation" of the RES led in particular instances to an enhanced tolerance of drastic shock. Exceptions to the latter were encountered however.

Materials and Methods

The term "blockade," as used in the present report, refers to the condition which exists following the administration of large amounts of colloidal suspensions into the circulation. These materials are rapidly removed from the blood stream by the phagocytes of the liver and spleen, so that by the end of about 2 hours, with the proper dose, they were no longer in the circulation. Thereafter, for a period up to 4 to 5 hours, the reticulo-endothelial elements showed a marked decrease in their capacity to phagocytize colloidal material. Blockade was achieved by the intravenous injection of a special suspension of carbon in gelatin (32 mg./100 gm. of body weight), or of saccharated iron oxide (proferrin—8.0 mg./100 gm.). The effectiveness of the blockade was verifed by the method of Biozzi, Benacerraf, and Halpern (6). In essence, the rate at which a standard dose (8 mg.) of carbon was removed from the blood stream was determined photocolorimetrically in serial samples and expressed on the basis of the ratio of the weight of the liver and spleen to total body weight (See Table IV). Since maximal interference with the phagocytic clearance of the blood stream was usually present from 1 to 4 hours after the injection of the particulate material, the animals were challenged with either graded hemorrhage or drum trauma during the 2nd or 3rd hour.

In another set of experiments, overloading of the RES was induced during shock by the infusion of *denatured crystalline albumin (bovine)*. The method of preparation was that used by Benacerraf *et al.* (7). A 1 per cent solution of crystalline albumin (Armour) in isotonic saline was adjusted to pH of 7.0 and heated in a water bath to 80–85°C. for approximately 20 to 30 minutes until there was a change in optical density (read at 550°A at 0.1 units in a 1 cm. cell). The pH was then brought to 5.4 or below and the precipitate centrifuged down. The precipitate was washed with saline at the same pH, and then dissolved in 1 per cent saline. Merthiolate was added (1:10,000) as a preservative. The final concentration was 30 mg./ml. and each rat received 1 ml./100 gm. of body weight.

A number of colloidal agents were given repeatedly for several days, a procedure which according to Benacerraf *et al.* (5) led first to a depression of phagocytic uptake and subsequently to a more rapid removal of particulate colloids from the circulation. In each instance, the capacity to clear the circulation of a standard dose of carbon was checked as a measure of the relative increase in phagocytic activity.

In one set of experiments, *saccharated iron oxide*, 2.0 mg. of proferrin (Sharp & Dohme, Inc., Philadelphia) or *iviron* (British Schering, England) was injected intravenously on 4 successive days.

In another series of animals, an *albumin globulin complex* (CAG)[2] was used. This material represents a heat-denatured fraction prepared from rabbit serum by the method of van der Scheer *et al.* (9). Fresh serum was heated to 60°C., the pH adjusted to 5.9–6.0 with N HCl, and dialyzed in a Visking membrane against distilled water for 24 hours. The precipitate was brought down by centrifugation, washed with distilled water at pH 9.0, and dissolved in 1 per cent saline by bringing the pH to 8.0. Merthiolate (1:10,000) was added as a preservative. The final concentration in different preparations was between 50 and 60 mg./ml., as determined by protein analysis on heat-dried aliquots after precipitation with trichloracetic acid. Each rat received intravenously 30 mg./100 gm. of body weight twice daily for 3 days.

Zymosan, an extract of yeast (Standard Brands, Stamford) used in properdin studies (8) was suspended in 1 per cent saline and a single injection of 1.0 mg./100 gm. given intravenously.

The remaining agents required no special preparation and were administered as indicated in the appropriate tables. Extracts of *Escherichia coli* prepared by the method of Landy and Johnson, as described in reference 10, by Difco Laboratories were used as the bacterial endotoxin.

Hemorrhagic shock was induced under rigidly controlled aseptic conditions in a CF Nelson strain of rats weighing between 130 and 180 gm. The animals were anesthetized with 3.0 mg sodium pentobarbital/100 gm. of body weight, and subjected to graded bleeding *via* the carotid artery by a self-adjusting bleedout reservoir system (11). Different degrees of hypotension were used, as indicated in specific experiments. Following blood replacement, the neck incision was closed and survival observed for 24 to 48 hours.

Trauma was produced by rotation in the Noble-Collip drum (12). The animals in this weight range showed an LD_{50} with 650 revolutions. The development of resistance to trauma (13) was achieved by exposing the animals to 300 turns on alternate days for a period of 8 to 10 days. These rats could then tolerate 850 revolutions in the drum with a 5 to 10 per cent lethal outcome, in contrast to controls which showed a 80 to 95 per cent lethality with this amount of trauma.

RESULTS

Blockade with Colloidal Suspensions

Blockade with colloidal materials has been demonstrated to have a deleterious effect on the course of the traumatic shock syndrome in both normal animals and in resistant rats, in which this form of pretreatment abolished the adaptation or resistance engendered by repeated exposure to sublethal episodes of drum trauma (14). It was therefore of interest to determine what effect these colloids would have on the acquired tolerance to bacterial endotoxins and the cross-tolerance resulting therefrom.

Effect on Tolerance to Endotoxin.

Several groups of rats were treated for 5 to 7 days with extracts of *E. coli*, as in the preceding paper of this series (15), as a means of inducing a tolerance to normally lethal doses of endotoxin. In each instance, the group was divided into a control and experimental category. The latter animals were given either 32 mg./100 gm. of the carbon-gelatin suspensions or 8.0 ml./100 gm. of saccharated iron intravenously. 2 hours later both groups received 4.0 gm. of *E. coli* extract intraperitoneally.

The findings listed in Table I clearly show the almost complete loss of tolerance in the "blockaded" group. The colloid-treated animals became obviously ill within 1 to 2 hours and most of the animals were dead by the end of 3 to 4 hours. The small

[2]GAC, albumin globulin complex.

intestines were atonic and distended. Large segments of the jejunum and ileum showed diffuse hemorrhage and frank blood in the lumen. The lymph nodes were prominent and hemorrhagic, particularly those in the mesentery and cervical region. The liver and kidneys were mottled and congested.

Loss of Cross-Tolerance.—As previously indicated (15), the establishment of tolerance to *E. coli* endotoxin in the rat is associated with the simultaneous appearance of resistance to both hemorrhagic and traumatic shock. The

TABLE I

Effect of Lethal Doses of Extracts of E. coli on Endotoxin-Tolerant Rats

	Survival*		
	A	B	C
Untreated	6/6	5/6	4/6
Carbon‡	0/6	1/6	0/6
Proferrin	1/6	2/6	0/6

* 4.0 mg. *E. coli* extract (Difco) injected intraperitoneally.

‡ See text for dosages and time interval.

TABLE II

Loss of Cross-Tolerance Following Pretreatment with Colloidal Suspensions

	Survival following drum trauma*	
Normal rats	2/20	(10 per cent)
Endotoxin-tolerant	18/20	(90 per cent)
Endotoxin-tolerant and carbon‡	1/18, 2/18	(17 per cent)
Endotoxin-tolerant and proferrin	3/18, 4/18	(19 per cent)

* 850 revolutions in Noble-Collip drum.

‡ See text for dose and time interval.

effects of colloidal carbon and saccharated iron oxide on the resistance to drum trauma were studied in the following experiment.

Two groups of 36 endotoxin-tolerant rats each were made tolerant by repeated injections of *E. coli* endotoxin as in the preceding experiments. One group was injected intravenously with colloidal carbon (32 mg./100 gm.) and the other with proferrin (8.0 mg./100 gm.). Twenty normal rats, and 20 endotoxin-tolerant rats not injected with colloidal material, served as controls. Control and experimental animals were then subjected to drum trauma 2 hours later, 850 revolutions being used as the test challenge. The results are shown in Table II.

The resistance to traumatic shock was markedly reduced in the tolerant rats given colloidal carbon or proferrin, with vulnerability in these animals which approached that of controls.

Exacerbating Action of Colloidal Agents on Irreversible Trend following Hemor-

rhage.—Experiments with graded hemorrhage were conducted to ascertain whether blockade with colloids also interfered with the capacity of endotoxin-tolerant rats to withstand this form of shock.

Twelve endotoxin-tolerant rats, which had been given carbon (32 mg./100 gm.), were kept for 3 hours at drastic levels of hypotension (1 hour at 65 mm. Hg and 2 hours at 35 mm.). This form of hemorrhagic hypotension is well tolerated by endotoxin-tolerant rats (see previous paper). All of the pretreated animals succumbed before the end of the 3 hour period of hypotension and spontaneously took up all of the blood in the reservoir system. Autopsy revealed marked congestion of the liver and considerable amounts of blood in the intestinal tract, as well as in the wall of the duodenum, jejunum, and cecum.

In another set of experiments, denatured crystalline serum albumin was used to study the effects of RES blockade.

Shock was induced in 10 rats by graded hemorrhage designed to yield in controls a 30 to 40 per cent lethal outcome. The animals received a priming dose of 30 mg./100 gm. of the denatured albumin intravenously and then a continuous infusion was begun for a period of 1 hour by a motor driven microburette which delivered 0.015 ml. of a 1 per cent solution/minute.

When administered during either the 1st or 2nd hour of the hypotensive episode, the albumin produced no immediately discernible changes in the output of blood, or evidence of a decompensatory uptake. The animals, however, did not respond to blood replacement measures. In all instances, the blood pressure was restored only to between 70 and 80 mm. Hg and fatal shock developed within 3 to 12 hours (10/10 died). A set of 6 control animals similarly treated, except that they were infused with untreated crystalline albumin, showed excellent recovery (5/6 survived).

Synergistic Effect of Colloidal Blockade and Endotoxin on Shock Reaction.—The data suggest that an impairment of the phagocytic function of the RES during the shock syndrome may serve to increase the sensitivity to bacterial endotoxins and thereby further the development of irreversibility. The possible consequences of such a situation on the pattern of vascular behavior following hemorrhage were examined by a combination of RES blockade and endotoxin.

A comparatively non-lethal episode of hemorrhagic hypotension (65 mm. Hg for 1 hour, 45 mm. Hg for 2 hours) was used as the standard challenge. In selected instances, the mesentery was exposed to permit observation of the microcirculation.

The administration of 32 mg. of carbon-gelatin, although deleterious, was not sufficient by itself to convert the reaction into a lethal form of shock. However, when the pretreated animals were infused at any point during the syndrome with small amounts of *E. coli* endotoxin by a motor-driven microburette (a total of 100 to 150 μg. delivered intravenously at a rate of 15 to 20 μg./minute for 1 hour), there was an immediate effect on the compensatory readjustment to blood loss. Thus, in six experiments, when the bacterial endotoxin was infused after only 1 hour of moderate hypotension, five of the rats showed an immediate decline with as little as 30 μg. of

extract and died before the end of the usual 3 hour shock period. Only one rat survived sufficiently long to be given a blood transfusion, but died 1 hour later.

Six animals were treated with the carbon-gelatin suspension and then subjected to hemorrhage with the mesocecum exposed for microscopic study. As indicated in a previous study (16), animals bled after carbon had been administered, showed a blunted compensatory reaction with a much reduced hyperreactivity in the terminal vascular bed. In the present experiments, the reactivity of the arterioles and precapillaries to epinephrine was increased only 6- to 8-fold, in contrast to the 50- to 100-fold shift in reactivity in untreated controls. An infusion of endotoxin was begun at this point and within 15 minutes the terminal arterioles and precapillary sphincters showed a continuous shift in reactivity towards the vasoinhibitory side, until the vessels became unresponsive to epinephrine (usually in about 60 to 75 minutes) and were visibly dilated. Despite the fact that the arterioles and precapillaries became refractory to the vasoconstrictor action of epinephrine, the small venules remained unaffected, leading to a highly unusual situation in which the venous vessels were the most reactive components of the terminal vascular bed. Vasodilation and capillary congestion became even more exaggerated following blood replacement. The rapidity with which these changes developed in the colloid-treated animals more closely resembled the situation encountered in the irreversible phase of hemorrhagic shock, than did the changes induced in animals primed with endotoxin alone.

Effect of Repeated Injections of Colloidal Particulates Cleared by the Reticulo-Endothelial System

A number of observations suggested that the adaptation to shock might also be associated with an altered status of the reticulo-endothelial elements. Histological inspection revealed that the Kupffer cells in the livers of drum-resistant rats were unusually large and prominent, indicating a hypertrophy of these elements. The fact that these cells became engorged with carbon or iron particles during blockade experiments and that this was associated with a loss of tolerance to shock also pointed to some involvement of the reticulo-endothelial elements in the adaptive reaction to trauma.

It has been reported (5) that exposure to different, apparently unrelated agents such as denatured serum proteins, colloidal suspensions and certain polysaccharides, leads to an adaptive, augmented response on the part of the RES, as manifest by a hyperreactivity of the phagocytic behavior of these cells. Biozzi, Benacerraf, and Halpern (6) were able to measure the relative efficacy of various procedures by determining the rates at which standard amounts of carbon were cleared from the bloodstream. The same method was used to verify the stimulating reaction in the present experiments.

Rats were subjected to drum trauma after pretreatment with four different agencies known to increase the phagocytic activity of the RES. The results of these experiments are listed in Table III, together with two groups of albumin-treated animals which showed no change in RES activity and served as controls. The degree of RES stimu-

lation which was achieved is indicated in Table IV by the K or alpha values, K representing the rate of clearance with respect to time and alpha the corrected value relative to the weight of the liver and spleen. Rats which had been treated with denatured serum proteins (CAG) showed the greatest increase in phagocytic function. These animals and those receiving repeated small doses of saccharated iron oxide were found to be unusually resistant to normally lethal doses of drum trauma. Crystalline albumin and ovalbumin had no effect on RES phagocytic function and, as can be seen, had no influence on the capacity to withstand trauma.

TABLE III

Tolerance to Drum Trauma Following Exposure to Factors Increasing Phagocytic Activity of RES

	Amount (per 100 gm. body wt.)	No. of days treated	Interval before trauma*	Survival
			hrs.	
None	—	—	—	4/20 (20 per cent)
Crystalline albumin (bovine)	25 mg.	3 (each 2×)	24	1/10 10 " "
Crystalline ovalbumin	5.0 "	5	24	4/20 20 " "
Saccharide iron oxide	2.0 "	4	24	17/24 70 " "
Denatured serum proteins (CAG)	25 "	3 (each 2×)	24	14/20 70 " "
Zymosan	1.0 mg.	1	24	6/15 (40 per cent)
	1.0 "	1	72	18/20 90 " "
	1.0 "	1	120	3/10 30 " "
Cold	2°C.	5	24	0/10 (0)
	2 "	5	72	7/10 (70 per cent)
	2 "	5	120	4/10 40 " "

* 850 revolutions in Noble-Collip drum.

Exposure to cold (2°C.) led to a biphasic sequence. When the animals were chilled for 5 days and exposed to drum trauma within several hours after removal, all the rats succumbed. Carbon clearance values at this time indicated a depressed or subnormal phagocytic activity. On the other hand, after 48 to 72 hours had elapsed, these animals were found to have become resistant to traumatic shock, coincident with a measurable increase in the clearance rate, as indicated by the K and alpha values.

The polysaccharide zymosan was included because of several considerations. Pillemer and associates (8) have used this extract of yeast as a means of reducing complement and properdin levels in the blood. Inasmuch as the material forms a colloidal suspension, it was suspected that it might also be cleared from the blood stream by the RES. The fall and subsequent rebound in properdin titers (24 to 72 hours later) described by these workers (17) resembles the initial depression and

secondary stimulation in RES phagocytic function encountered with colloidal particulates in general.

The present experiments brought to light several interesting points concerning properdin titers[3] and the reaction to shock in colloid-treated animals. Rats, pretreated with 32 mg./100 gm. of carbon, were found to show during the period of RES blockade unusually low blood titers of properdin (12 units/ml. as contrasted with 18 to 24 units/ml. in controls). Zymosan, on the other hand, led to a fall in properdin levels (3 units/ml.), which was not associated with a change in the phagocytic function of the RES (see K and alpha values in Table IV). In both of these instances, the

TABLE IV

Phagocytic Function of RES as Measured by Clearance of Carbon from Circulation

	No. of rats	Interval before test	K	$\frac{\text{Body wt.}}{\text{Wt. L \& S}}$	α
		hrs.			
Controls	22	—	0.022 (±0.01)	25.5	6.9 (±0.8)
Saccharide iron oxide (8.0 mg.)	6	3	0.010	24.7	5.4
Denatured serum proteins (CAG) (25 mg. × 2, 3 days)	10	24	0.081	21.8	9.2
Endotoxin-tolerant	7	72	0.040	25.0	8.1
Drum-resistant	14	72	0.017	26.0	6.7
Zymosan (1.0 mg.)	4	3	0.026	24.6	7.2
" " "	4	24	0.040	24.0	8.1
Cold (2°C., 5 days)	6	24	0.028	26.0	7.7

K, slope of carbon clearance curve (8 mg. intravenously).

α, K corrected for weight of liver (L) and spleen (S) relative to body weight.

$$\alpha = \frac{W}{WL + S}\sqrt[3]{K}$$

animals were clearly more susceptible to traumatic and hemorrhagic shock. On the other hand, during the second phase of the zymosan reaction, which appeared 48 to 72 hours later, properdin titers were high (24 units/ml.) and RES phagocytic function was augmented. As indicated, these animals were able to withstand abnormally large amounts of drum trauma.

The protective action of the zymosan pretreatment was equivalent to that engendered by tolerance to bacterial endotoxins. The major difference was the fact that tolerance to trauma following zymosan was short lived, being no longer evident after 96 hours, whereas a single course of endotoxin tolerance continued to exert a cross-reaction for periods up to 6 to 7 days.

A small number of corroborative experiments were conducted with graded hemorrhage during the secondary rebound at 72 hours after zymosan and after treatment

[3] Properdin titers were determined through the generous cooperation of Dr. Louis Pillemer on coded serum samples.

for 4 days with repeated doses of saccharated iron. A lethal episode of hemorrhagic hypotension (1 hour at 65 mm. Hg and 2 hours at 35 mm. Hg) was used as the test challenge. Following zymosan (1 mg./100 gm.), 80 per cent of the rats (4/5) survived and with colloidal iron oxide, 100 per cent of the rats (5/5) survived in contrast to only 25 per cent of the untreated controls (1/6, 2/6).

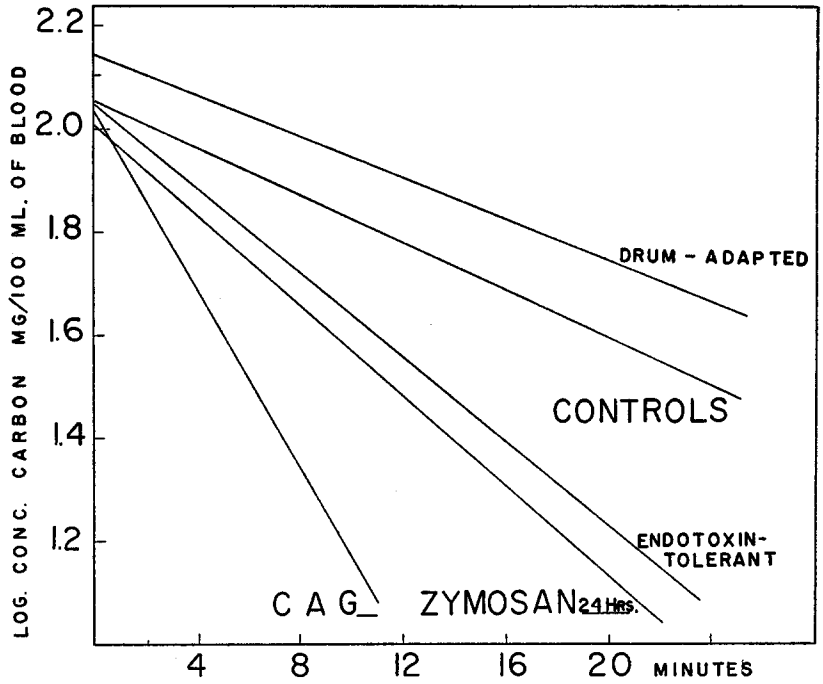

FIG. 1. A comparison of the phagocytic activity of the RES, in the various experimental categories subjected to shock, as measured by the rate of clearance of carbon from the blood stream. The graph was reconstituted by taking average values (4 to 10 animals in each category) for the slope (K) and using the average concentrations of carbon at 2 minutes as the point through which the intercept will pass. The K values for the drum-adapted animals are 0.017, for the controls 0.022, for the endotoxin tolerant rats 0.040, for zymosan at 24 hours 0.040, and for CAG 0.081. The CAG rats show the most rapid clearance of carbon, whereas the drum-adapted animals fall somewhat below the controls, despite the fact that both groups are equally tolerant of shock.

Phagocytic Function in Endotoxin and Drum-Tolerant Animals

Inasmuch as the adaptive reactions to agencies such as colloidal aggregates, repeated trauma, and bacterial extracts, led in each case to an enhanced tolerance to shock, the possibility was entertained that the latter two procedures might also be associated with an augmented phagocytic function of the RES. Measurement of the rate of carbon clearance from the bloodstream was therefore made in these animals, at 72 to 96 hours after the final challenging dose. The data presented in Fig. 1 show a

clear-cut enhancement of phagocytic uptake in the endotoxin-tolerant animals, but not in those adapted to drum trauma. Many of the trauma-resistant rats showed clearance values which fell within the lower range of normal.

DISCUSSION

In further pursuit of the factors influencing the course of epinephrine reactivity during the shock syndrome, data have been accumulated which indicate that the lethal consequences of bacterial endotoxins, hemorrhage, or trauma are regularly associated with an altered behavior of the reticulo-endothelial system.

There is always the possibility, since we are dealing with correlative data, that the changes being measured in the RES have no direct bearing on the course of events leading to circulatory collapse during the shock reactions. One must, however, take into account the fact that identical changes were induced by a diversity of agencies, unrelated except in so far as they were colloidal in nature. The evidence becomes highly persuasive when one considers the regularity with which on the one hand, decompensatory reactions were exacerbated with blocking doses of colloidal particulates and on the other, an enhanced tolerance to lethal shock was engendered by regimes which increase the phagocytic clearance of colloids from the blood stream. At the very least, the evidence would seem to indicate that some facet of behavior of the RES is concerned with the vascular manifestations of the shock reaction—even though this relationship may not depend directly upon the phagocytic function of the reticulo-endothelial elements.

The present studies indicate that the increased susceptibility to bacterial endotoxins, observed during the course of the conventional shock reaction, could be reproduced by pretreatment with colloidal carbon or iron, presumably through interference with the reticulo-endothelial elements. The susceptibility to endotoxin is reflected by the rapidity with which the vessels in the microcirculation become hyporeactive when bacterial extracts are infused. Since it was possible to convert the state of hyperreactivity during shock to one of hyporeactivity by the administration of blocking doses of colloids, such an impairment could conceivably be the basis of the vasculo-toxic sequelae encountered during this phase of the shock syndrome.

Although controversial, the literature contains numerous reports to support this assumption. Separate investigations have shown that agencies such as infection (18), excess cortisone (19), or acute exposure to cold (20), interfere with the activity of the RES. Each of these contingencies has in turn been found to impair the capacity to withstand hemorrhage or trauma. The interdependence of these factors was substantiated in recent shock experiments in which rats were exposed to drum trauma following overdosage with cortisone (14), or subjected to graded hemorrhage in the face of infection, as contrasted to animals bled under aseptic precautions (21). In each of these instances,

vascular decompensation and hyporeactivity became unusually prominent following procedures which were non-lethal to controls and which were not associated with a falling off in epinephrine reactivity in the microcirculation of the mesentery.

The mechanism whereby an augmented phagocytic activity of the RES influences the vascular response to shock remains speculative. The obvious implication is that these elements now handle more effectively agents such as bacteria, bacterial endotoxins, tissue metabolites, etc. Such an explanation would still leave unanswered the basis of the adaptive changes in the terminal vascular bed proper, such as resistance to direct injury, absence of capillary damage, and refractoriness to the local effects of bacterial endotoxins.

Mention should be made of our findings in reference to the properdin system, which has been suggested as a possible factor for the increased susceptibility and tolerance to hemorrhagic shock (22), drum trauma (23), and the lethal effects of bacterial endotoxins (24). As in the case of pretreatment with zymosan (17), colloidal blockade with carbon leads to low titers of properdin in association with poor tolerance to hemorrhagic hypotension and drum trauma. Drum-resistant or endotoxin-tolerant rats did not show higher levels of properdin than normal animals. Furthermore, following exposure of resistant animals to drum shock, the properdin levels fell to a low of 3 to 6 units/ml., despite the fact that these animals did not go into fatal shock.

Admittedly, a shift in emphasis to the reticulo-endothelial system does not appreciably advance our knowledge of the basic defects involved in different forms of shock. Aside from measurements of the phagocytic activities of the RES, little is known concerning the physiological potential of this ubiquitous system. The observations on this system demonstrate the existence of a consistent, predictable pattern of change both in the conventional shock syndrome and that produced by bacterial endotoxins, wholly compatible with the identity of these two experimental entities.

SUMMARY

In studies designed to establish the interrelationship between bacterial endotoxins and the vascular sequelae of hemorrhagic and traumatic shock, the effect of factors known to influence the phagocytic behavior of the reticulo-endothelial system (RES) were investigated.

Measures which induced a so called "blockade" of the RES were uniformly associated with an exacerbation of the vascular effects of the endotoxin of *E. coli*. Such pretreatment also counteracted the cross-tolerance induced by endotoxins against the lethal effects of hemorrhage or drum trauma.

The vascular reactions characteristic of irreversible hemorrhagic shock could be simulated by a combination of pretreatment with carbon or proferrin and the infusion of small doses of *E. coli* endotoxin.

An increase in the phagocytic activity of the RES, induced by repeated

injections of certain colloids, was associated with an enhanced tolerance of shock.

Measurement of carbon clearance values indicated that although an augmented phagocytic capacity was present in rats with induced tolerance to bacterial endotoxins, the development of resistance to trauma was not associated with a comparable change in the phagocytic function of the RES.

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