CARE OF THE CRITICALLY ILL CHILD:
ENDOTOXIN SHOCK

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For practical purposes we may consider that endotoxins of gram-negative bacteria are the cause of endotoxic shock. In general, endotoxins are produced by bacteria which form smooth colonies. However, it should be mentioned that small quantities of endotoxin have been found in colonially rough, gram-negative rods and in some gram-positive bacteria.

Endotoxins are found in the outer layers of the bacterial cell wall. They are so closely associated with other constituents of this structure that their isolation requires strong chemical treatment. Endotoxins are macromolecules which readily form complexes with each other and with other macromolecules. The two major constituents of endotoxins are lipids and polysaccharides. Endotoxins also contain a small percentage of peptides, so we may consider that endotoxins are lipid-polysaccharide-peptide macromolecules. All endotoxins contain phosphorus also. The polysaccharide moiety is composed of a number of different carbohydrates, such as glucose, galactose and mannose, as well as pentoses, heptoses, and hexosamines. Also present are di-deoxy hexoses, which are found only in endotoxins.

The lipid moiety contains even-numbered saturated and unsaturated fatty acids. The chemical constituents of endotoxins are arranged in three major zones in the macromolecule: the polysaccharide, the lipid-rich, and the amino acid-rich moieties. The backbone of the molecule is polysaccharide, to which are attached amino acids. The fatty acids are also attached to the carbohydrate backbone; these are ester bound to OH groups or amide bound to NH groups of the carbohydrate, probably through such compounds as glucosamine. The endotoxin molecule is unique in its fatty acid-carbohydrate linkages, which have not been found in any other natural substance. Phosphoric acid is found in both the lipid and carbohydrate moieties.

Endotoxins elicit, directly or indirectly, a large number of reactions affecting many organ systems of the host. It seems very likely that most of these toxic reactions are caused by the presence of the lipid moiety, particularly the long chain fatty acids. Rough mutant, gram-negative bacteria (which contain no polysaccharide moiety) have been shown to contain endotoxins which have full endotoxic action. The polysaccharide moiety probably corresponds to the O antigen of the gram-negative bacilli. This portion of the macromolecule determines the serologic specificity of the organism. The peptide moiety appears to have little, if any, endotoxic activity, since removal of this portion of the molecule does not decrease its endotoxic potency.

Although endotoxins have a basic general structure, it should be noted that there is no single type of endotoxin molecule. Several fully active, chemically different molecular complexes may be found in endotoxins prepared from one bacterial culture. Whether or not these different molecules act in exactly the same manner is not known. The greater the heterogeneity of the endotoxin preparation, the greater is its toxicity. It is probable that a number of organs and more than one kind of organelle may be targets for endotoxin. Different endotoxin molecules may injure different cells.
or different subcellular elements simultaneously, or they may act in sequence. If the latter is the case, a chain reaction might result.  

Endotoxin is found soon after its injection into animals in the cells of the reticulo-endothelial system. About 90% of the endotoxin appears in the liver and spleen, but endotoxin also accumulates in the endothelium of blood vessels and in the alveoli of the lungs. Endotoxin is adsorbed to the surface of polymorphonuclear leukocytes (or it is actually present in the cytoplasm of these cells) within 10 minutes after it has been injected intravenously. Endotoxin quickly becomes adsorbed to platelets but not to erythrocytes.

**BIOLOGIC EFFECTS OF ENDOTOXINS**

Endotoxins elicit many of the reactions which we sum up in the term inflammation. These include local vasodilatation, increased vascular permeability which permits plasma and leukocytes to leave the capillaries, enhanced phagocytosis, and stimulation of host resistance. However, many of the reactions caused by endotoxins are not related to inflammation. These include the following:

1. Mobilization of interferon by endotoxin.
2. Induction of the local and generalized Shwartzman reactions.
3. Endotoxin, by a number of mechanisms, causes alterations in the systemic blood pressure which may lead to fatal shock. These actions include the release of kallikreins from leukocytes with the consequent production of kinins, the alteration of the action of epinephrine and norepinephrine on blood vessels, and the release of histamine from mast cells.
4. Endotoxin causes a biphasic febrile reaction; the second peak is probably due to release of an "endogenous pyrogen" from leukocytes.
5. Endotoxin induces leukopenia followed by leukocytosis.
6. Endotoxin causes a fall in number of circulating platelets.
7. Endotoxin causes injury to endothelium of blood vessels.
8. Endotoxin may cause widespread intravascular clotting, with fibrin formation. In this condition there occurs a decrease in circulating platelets, prothrombin, fibrinogen, and intrinsic clotting factors V and VIII. Intravascular clotting may be initiated by activation of Hageman factor (XII) by endotoxin injury of endothelium of blood vessels.
9. Endotoxin causes deleterious changes in carbohydrate and protein metabolism.
10. Endotoxin causes hemorrhagic necrosis in tumors, probably by injury to blood vessels.
11. Mice are protected from a lethal dose of radiation by preceding injection of endotoxin.

It is clear from the very extensive literature on the subject that endotoxins are directly responsible for the shock which occurs during the course of infection with gram-negative bacteria. Changes in the cardiovascular system due in part at least to altered response of the blood vessels to vasoactive substances play an important part in the fatalities which occur in such infections. In addition, extensive intravascular clotting is obvious in some instances, and it is quite possible that some degree of intravascular clotting occurs in all instances. It is also certain that deleterious changes in metabolism occur in many instances, and there is evidence that these alterations are accompanied by cell and organelle injury.

**EFFECTS OF ENDOTOXIN ON CARDIOVASCULAR SYSTEM**

We shall consider first the circulatory changes which are induced by endotoxin. Some confusion has resulted from the fact that endotoxin affects the circulatory system somewhat differently in different animal species. For example, endotoxin brings about the pooling of a large volume of blood in the portal system of the dog, but this does not occur in the monkey. Another factor which has produced conflicting data
is the use of anesthesia in some experiments and not in others. This variance may be due to the fact that anesthetics alter the normal circulatory reflexes and may alter the effects of endotoxin. Also, the sequence of the events observed is dependent on the dose of endotoxin used. Finally, the circulatory changes which occur early in the course of endotoxic poisoning may be different from those which are observed later.

It is clear from experiments conducted on unanesthetized rhesus monkeys that the initial response to endotoxin is a decrease in systemic blood pressure which is due to a decrease in peripheral arterial resistance. The decrease in arterial resistance is accompanied by an increase in venous tone. Arterial resistance is decreased in all organs except the spleen, indicating that the microcirculation in the monkey does not undergo selective constriction on exposure to endotoxin. This suggests that the entire microcirculation is involved in potential pooling of blood in the early phase of shock.8

Coincident with the peripheral vascular changes, an increase in heart rate and a decrease in cardiac output occur. The decrease in cardiac output reverts in 2 to 3 hours to normal or rises to above normal values.

Wilson and his colleagues have presented evidence which suggests that the early phase of shock in patients with bacteremia caused by gram-negative organisms is very similar to that seen in endotoxin shock in the rhesus monkey.9 It has been shown that the early phase cardiovascular changes induced by endotoxin in monkeys are accompanied or slightly preceded by the appearance of kinins in the plasma.10 Recent findings support the belief that kinins may have an essential role in the early phase of endotoxin shock. These include the observation that infusion of kinins in man is followed by all the changes seen in the early phase of endotoxin shock.11 The fall in blood pressure observed in the early phase of endotoxin shock is due almost entirely to a decrease in peripheral vascular resistance. Kinins are the most potent endogenous vaso-dilating agents known. The concentration of kinins in the plasma of monkeys injected with endotoxin is sufficient to cause the vasodilation and fall in blood pressure observed in them.

Nies and his co-workers10 made serial measurements of plasma kinin concentration in the early phase of endotoxin shock in the unanesthetized monkey. Kinin concentration rose from the normal state, in which no kinin is detectable, to concentrations which were as high as 29 ng/ml. The kinins appeared in less than 15 minutes after intravenous infusion of endotoxin was begun (the infusion was conducted over a period of 40 minutes). The appearance of kinins in the plasma preceded or coincided with the beginning of the fall in blood pressure and the decreased peripheral resistance which were observed. The peak concentration of plasma kinin was reached in 1 to 2 hours, and it returned to undetectable levels in the monkeys which survived the dose of endotoxin. Plasma kinin concentration remained slightly elevated for 24 hours in the monkeys which did not survive. As might be expected, plasma concentration of kininogen (the globulin precursor of kinin) fell as the kinin level rose and returned toward normal values as kinin disappeared from the plasma. Kinins have a short survival time in plasma; they have a half life of about 30 seconds. They are destroyed by a kininase (carboxypeptidase-N). In the experiments of Nies, et al.10 described here, kininase remained elevated for at least 24 hours in the monkeys killed by the endotoxin, but very little rise was seen in animals which survived.

In the later (second) phase of endotoxin shock in the unanesthetized monkey, peripheral resistance is elevated rather than greatly reduced, as it is in the first phase. Also, unlike the earlier phase, cardiac output is decreased in the second phase of shock. Kinin concentration is not elevated in the second phase. Therefore, other vasoactive substances must be involved in the later stages of endotoxin shock. It is prob-
able that epinephrine and norepinephrine are involved in the later stages of shock, while it is clear that kinins and possibly histamine play a key role in the cardiovascular changes in the early phase. Kinins have been shown to have a number of interesting inter-relationships with epinephrine, norepinephrine, and histamine, which we shall describe later in this discussion. It is possible that the effect of kinins in the first phase of endotoxin shock determines the occurrence and severity of the later stages of shock. For this reason, a brief discussion of kinins may be useful.

Kinins are linear polypeptides, having from 9 to 11 amino acids and a molecular weight a little over 1,000. The two best studied kinins are bradykinin, which is made up of nine peptides, and kallidin, which has the same nine amino acids in the same order as bradykinin, as well as a tenth amino, acid-lysine. The structure of these two kinins is shown in Figure 1.

The precursor of kinins are kininogens, which are alpha-2-globulins present in plasma. Kinins are split from kininogens by the action of enzymes called kallikreins, which are present in granulocytes. Hageman factor may be activated as a consequence of injury to vascular endothelium. The sequence of reactions outlined here may be set off by the injury to endothelial cells of blood vessels which endotoxin causes. Furthermore, there is no doubt that kinins are produced by the action of endotoxin on granulocytes. This is probably brought about by the release of kallikrein (or a kallikrein activator), which is present in granulocytes. Kinins in nanogram quantities cause vasodilation of the arterioles of the systemic circulation, including cerebral and coronary vessels. They very probably, at least in part, cause the systemic vascular dilatation and the fall in blood pressure which occurs in the early phase of endotoxin shock. However, kinins are not found in the plasma for

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**Fig. 1.**

<table>
<thead>
<tr>
<th>Bradykinin</th>
<th>Kallidin</th>
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<tbody>
<tr>
<td>Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg</td>
<td>Lys-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg</td>
</tr>
</tbody>
</table>

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**Fig. 2.**

1. **HAGEMAN FACTOR** ➔ **ACTIVATED HAGEMAN FACTOR**

2. **PRO-PERMEABILITY FACTOR/DILUTE** ➔ **PERMEABILITY FACTOR/DIL**

3. **KALLIKREINOGEN** ➔ **KALLIKREIN**

4. **KININOGEN** ➔ **KININ**

*Permeability factor/dilute is a protein found in serum which causes increased vascular permeability at site of injection into the skin.*

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[Image 65x30 to 547x762]
more than a few hours. They are not detectable in the plasma in the later stages of shock when there is an increase in peripheral resistance, decreased venous return to the heart, and greatly decreased cardiac output. Kinins may play an indirect part in the later phases of shock by setting in motion chemical changes which lead to the formation of other potent vasoactive agents. These include epinephrine, norepinephrine, and histamine. It is very probable that the first two compounds play a very important role in the vascular changes of endotoxin shock; the importance of histamine is not clear. Large doses of kinins release catecholamines by direct action on the medulla of the adrenal. A reciprocal relationship between catecholamines and kinins is suggested by the fact that norepinephrine and epinephrine have been shown to cause the formation of kallikrein from tissues. Norepinephrine causes the excretion of kallikrein from salivary glands, and epinephrine infusion of carcinoid tumors also brings about the production of kallikrein. Conversely, epinephrine enhances the action of kininase, thus increasing the destruction of kinin. It is possible that this is one mechanism which serves to control the plasma kinin production.\textsuperscript{12,14,15} It is of interest also that kinins cause the release of histamine from mast cells. It has been shown by Hinchshaw, Jordan, and Vick\textsuperscript{14} that histamine rises in the blood of monkeys given endotoxin. This rise accompanies the fall of blood pressure in the early stage of shock, beginning within 30 minutes after the injection of the endotoxin. In fatally poisoned monkeys, histamine remains in higher than normal concentration in the plasma for at least 10 hours. There is no direct proof that the serum histamine rise is brought about by the action of kinins, but this possibility cannot be excluded. That interactions exist between kinins and the vasoactive amines (histamine, epinephrine, norepinephrine, and serotonin) has been well established by experiments on man and laboratory animals. These relationships are shown in Figure 3, which is modified from a paper by Melmon and Cline.\textsuperscript{15}

It is probable that all these compounds play a part in the circulatory changes which are induced by endotoxin. Present knowledge indicates that kinins, epinephrine, and norepinephrine may be of more importance than histamine or serotonin. It was shown by Thomas\textsuperscript{16} in 1956 that epinephrine caused hemorrhagic necrosis of the skin in rabbits which had previously been given an intravenous injection of endotoxin. Mixtures of epinephrine and endotoxin injected into the skin caused similar lesions. These observations led to the examination of the possibility that some of the harmful effects of endotoxin might be due to the fact that it altered the reaction of peripheral blood vessels to epinephrine and norepinephrine. Zweifach, Nagler, and Thomas\textsuperscript{17} demonstrated that endotoxin does change the normal vasoconstricting action of epinephrine on blood vessels. Small doses of endotoxin cause epinephrine to exert a greatly increased degree of vasoconstriction. In the presence of endotoxin, prolonged and intense vasoconstriction is caused by a quantity of epinephrine which will normally have no effect on blood vessels. A large dose of endotoxin produces a reversal of this effect. With large doses of endotoxin, blood vessels fail to constrict or actually dilate when they are exposed to epinephrine. Similar results were obtained with norepinephrine.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig3.png}
\caption{Fig. 3.}
\end{figure}
Zweifach and his co-workers showed that, in the rat, application of threshold doses of epinephrine (0.2 to 0.4 ng per milliliter) induced transient constriction of terminal arterioles and capillaries, with brief stoppage of capillary blood flow. After 10 to 20 seconds the blood vessels resumed their normal caliber, and blood flow became normal. When endotoxin was given intravenously in small sublethal doses, the application of the same threshold dose of epinephrine caused intense, widespread constriction of arteries, arterioles, venules, and small veins and complete ischemia of the capillary bed. The venules and veins proved to be more reactive to the combination of endotoxin and epinephrine than were the terminal arterioles. The venous outflow from the capillary bed was completely stopped by quantities of epinephrine which had no effect on the arterioles.

When larger (lethal) doses of endotoxin were given, terminal arterioles and venules became totally unresponsive to epinephrine and norepinephrine, while the arteries and veins continued to be hyperreactive to these amines and remained greatly constricted. As a result, blood became pooled in all the distended capillaries and venules, while the arteries and veins were contracted to thread-like diameter. The distension of the capillaries and venules was followed by the appearance of petechiae.

We shall now consider in more detail the hemodynamic effects which the vasoactive compounds bring about. The changes which are observed probably depend upon which of these compounds (or which combination of them) is acting on the circulatory system at a given time. The amount of time which has elapsed after the beginning of exposure to endotoxin is also of great importance. The dose of endotoxin given, the species of animal studied, and the use of anesthesia all have an influence on the data which are obtained. When these factors are taken into account, we find that there is general agreement regarding many of the changes which have been observed following administration of endotoxin. There is a high degree of agreement among investigators concerning the alterations which occur soon after endotoxin is given to the experimental animal. In the anesthetized dog and the anesthetized and the unanesthetized monkey, the injection of endotoxin is very quickly followed by a fall in blood pressure. In the dog this is accompanied by a decrease in responsiveness of the precapillary vessels to vasoconstricting substances and an increase of responsiveness of the postcapillary vessels, which become greatly constricted. There is a marked rise in the total peripheral resistance. Blood becomes pooled in the mesenteric and portal venous systems, and venous return to the heart decreases. Cardiac output decreases, and blood pressure falls. This pooling phenomenon is always observed in dogs. In the unanesthetized monkey, injection of endotoxin is also followed by a prompt fall in blood pressure. Heart rate increases and cardiac output falls, but return to normal or even above normal values within 3 hours. In sharp contrast to the dog, the monkey experiences a fall in total peripheral resistance. This decline is roughly parallel to the decrease in blood pressure. No pooling of blood in portal, splanchnic, or other large areas is found in the unanesthetized monkey.

The decrease in venous return, which probably accounts for the lowering of cardiac output, is believed by some authors to be due to a net increase in the volume of blood in the small veins throughout the circulatory system. This would amount to a uniform pooling of blood, in contrast with the hepatosplanchnic pooling seen in the dog. As shock progresses in the dog, dilatation of the arterioles and capillaries progresses while constriction of the veins continues. Blood enters the capillary beds in increasing amounts but is unable to leave them because of the venous constriction. Hydrostatic pressure is increased in the capillary beds, forcing fluid and blood cells out of the circulatory system and into the tissues. Circulating blood volume is decreased and
perfusion of the organs is diminished. Hemorrhagic necrosis of the viscera occurs, with the intestinal mucosa suffering the most severe damage. Venous return to the heart falls further, causing more marked decrease of cardiac output and blood pressure.19,20

Late in the course of endotoxic shock in the unanesthetized monkey, circulatory changes occur which are different from those encountered soon after endotoxin has been injected. In this second phase, which may begin a short time before death, the total peripheral resistance is somewhat increased and cardiac output is decreased. Even at this point, however, no localized pooling of blood is found in the monkey.10

In man, endotoxin induces circulatory changes which in many ways resemble those it causes in the unanesthetized monkey. The effects on the human circulation are quite different from those suffered by the dog.

It is apparent that endotoxin causes a decrease in the total peripheral resistance (TPR) in the septic patient. Wilson and colleagues9 studied the TPR in 12 patients with septic shock uncomplicated by hypovolemia due to massive blood or fluid loss (hypovolemic shock) or by myocardial infarction (cardiac shock). Eleven of these patients with “pure” septic shock had a TPR which was lower than the normal value of 1,000 to 1,300 dyne-sec/cm²; one patient had a normal value, none had an elevated TPR. Similar results are reported by others.21

The patients with endotoxic shock studied by Wilson and co-workers9 had central venous pressure recordings in the normal range. This is in very sharp contrast to the findings in dogs.

Cardiac output has been described as showing a steady decline in patients with endotoxic shock.21 However, Wilson, et al.9 reported that this is not a uniform finding. Three of their patients had a normal cardiac output together with decreased TPR, five had an increased cardiac output, and four had a decreased cardiac output. The cardiac output appeared to be related to survival. Only a small percentage of patients with a cardiac index of 2.0 l/minute/square meter survived. The cardiac index is the cardiac output per square meter of body surface; the normal cardiac index is 2.5 to 3.75 l/minute/square meter.

Wilson, et al.9 showed that endotoxic shock differed from the shock caused by hemorrhage or other large-volume fluid loss (hypovolemic shock) and from the cardiac shock of myocardial infarction. This is summarized in Table I.

Every physician knows that the distinctions among the three types of shock made here often are not very sharp. In a significant number of patients, shock is caused by combinations of endotoxemia, blood and fluid loss, and cardiac disease. Such patients present clinical findings of great complexity. For example, when hypovolemic and endotoxic factors coexist, TPR may be either elevated (as it is in hypovolemic shock), decreased (as it is in endotoxic shock), or normal. Similarly, when myocardial

### TABLE I

<table>
<thead>
<tr>
<th>Findings</th>
<th>Endotoxic Shock</th>
<th>Hypovolemic Shock</th>
<th>Cardiac Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total peripheral resistance</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>Low, normal, high</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>Normal range</td>
<td>Low</td>
<td>High</td>
</tr>
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</table>
dial infarction complicates endotoxemia, TPR may be elevated, cardiac output may be decreased, and central venous pressure may be high.

**INTRAVASCULAR COAGULATION**

Thrombi have been found in the blood vessels of many organs in animals which have been injected with endotoxin. There are also many well documented examples of widespread intravascular clotting in patients with sepsis due to gram-negative bacteria, other bacteria, viruses, and rickettsial infections. Perhaps the bacterial infection which most often causes extensive intravascular coagulation is meningococcemia.

It has been demonstrated that endotoxin acts to disturb the intravascular clotting mechanism in a number of ways. Some of these effects we shall consider here. It has been shown by McGrath and Stewart that endotoxin injures the vascular endothelium of rabbits. Within 1 hour after these animals are given one dose of endotoxin intracardially, histologic changes are seen in the endothelium of systemic arteries. The normally elliptical nuclei of the endothelial cells become spindle shaped and stain irregularly. In some areas the endothelial cell nuclei show vacuolization, and a few red and white blood cells are stuck to the cell surface. Twenty-four hours later the damage is more severe; some of the nuclei are almost unrecognizable. In some parts of the arteries, all cellular structure is destroyed. Clumps of red cells and platelets are adherent to the surface of the injured endothelial cells.

The clear-cut evidence of almost immediate injury of the vascular endothelium is of interest in several ways. First, it is of importance in that it is probable that some injury to the endothelium is necessary for the formation of fibrin clots. Second, it is believed that injury to the endothelium may bring about activation of Hageman factor (coagulation factor XII), which begins the chain of reactions which culminates in the action of thrombin on fibrinogen to form fibrin.

After injection of endotoxin in animals, platelets decrease, probably due to formation of platelet thrombi. According to Hardaway, intravenous injection of endotoxin into the dog brings about the same widespread intravascular coagulation as does the injection of thrombin. However, thrombin causes clotting by direct action on fibrinogen, while endotoxin does not affect fibrinogen directly. Thrombin removes negatively charged peptides from fibrinogen, and the removal of these repelling charges permits the fibrinogen molecules to aggregate and form a fibrin network. Endotoxin probably starts coagulation by activating Hageman factor. Both agents bring about widespread coagulation in the microcirculation, which causes severe obstruction to blood flow. Hardaway has shown that, within 5 minutes after intravenous injection of endotoxin, the plasma of the dog has undergone a severe decrease in fibrinogen, prothrombin, and coagulation factors V, VII, VIII, IX, X, XI, and XII.

Similar decrease in the components of the intravascular clotting mechanism occurs in man in endotoxemic conditions. Decrease in circulating platelets, coagulation factors V and VIII, prothrombin, and fibrinogen have been demonstrated. Blockage of the circulation may be widespread, causing necrosis of large areas of skin. Occlusion of vessels large enough to require amputation of extremities may occur.

As soon as fibrin is formed, fibrinolysis begins. This is carried out by a proteolytic enzyme system—the plasminogen-plasmin system. Plasminogen is present in all body fluids, but the highest concentration is in the plasma. Plasminogen is always incorporated into fibrin deposits as they form. Plasminogen activators, which are also present in many body fluids, convert plasminogen to plasmin. Plasmin hydrolyzes fibrin into two large components which are antigenically distinct.

In many instances, soon after intravascular coagulation occurs, plasma fibrinogen is restored to normal or to higher than normal levels, and the platelets in the blood reach
or exceed their pre-coagulation number. However, in some instances fibrinogen and platelets are not restored in proper quantity while fibrinolysis continues, with the formation of compounds which interfere with the polymerization of fibrin. In this situation intravascular coagulation may be followed by severe bleeding into skin, mucous membranes, and internal organs.

**EFFECT OF ENDOTOXIN ON METABOLISM**

Endotoxin has an adverse effect on carbohydrate and protein metabolism. In addition, animals and patients with endotoxemia are usually in metabolic acidosis. These effects probably are in part the result of cell injury which is secondary to interference with the microcirculation. However, there is reason to believe that endotoxin causes direct injury to cells and cellular organelles. For example, the plasma concentration of the lysosomal enzyme alpha glucosidase rises within 2 hours after the unanesthetized monkey is given an injection of endotoxin. This indicates that the membrane of the lysosome has been injured sufficiently to allow the escape of an enzyme when changes in the microcirculation of the animal are not yet profound.

There is convincing evidence from animal experiments that endotoxin causes derangement of carbohydrate metabolism. It was shown by Berry and co-workers that mice given a large dose of endotoxin suffer severe depletion of blood glucose liver glycogen and total body carbohydrate. Endotoxin prevents the conversion of injected glucose into liver glycogen, but no effect on muscle glycogen is produced.

It has been shown that endotoxin interferes directly or indirectly with essential molecular reactions in carbohydrate metabolism. For example, endotoxin inhibits the oxidative decarboxylation of pyruvate. This was demonstrated in animals given salmonella or meningococcus endotoxins. Pyruvic acid (CH₃·CO·COOH) normally is converted to acetaldehyde by the enzyme carboxylase and the coenzyme carboxylase (thiamine pyrophosphate or TPP). Then, by a series of reactions involving lipoic acid, flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide (NAD), and coenzyme A (Co A·SH), it is converted to acetyl-coenzyme A. In this form ("active" acetate) it enters the citric acid cycle (Krebs cycle). The conversion of pyruvic acid to acetyl-coenzyme A may be summarized as shown in Figure 4. Endotoxin blocks this reaction. As a result, no pyruvate enters the Krebs cycle in the form of acetyl-coenzyme A, and further carbohydrate metabolism is greatly diminished. Since pyruvate cannot enter the Krebs cycle to be metabolized to ketoglutrate, it is metabolized to lactic acid to a greater extent than is normal. Lactic acid thus becomes the end product of the glycolytic glucose cycle. Accumulation of lactic acid may contribute to the acidemia seen in endotoxin shock. Furthermore, because of the decreased function of the Krebs cycle, fewer energy molecules pass through the cycle, and production of adenosine triphosphate (ATP) is reduced. Endotoxin may interfere with the pyruvate/acetyl coenzyme A reaction indirectly—by its effect on the microcirculation, which might
injure cell mitochondria. If this is the case, the reaction may be blocked by the breakdown of the cytochrome enzyme system, which normally accomplishes the final step in the removal of the hydrogen produced. Or, endotoxin may interfere with enzymes by directly injuring mitochondria.

There is in fact evidence that endotoxin does damage liver mitochondria. Endotoxin causes a decrease in the oxygen uptake of rat liver mitochondria, and it uncouples oxidative phosphorylation in these organelles.

Endotoxin has also been shown to have effects on protein metabolism. It inhibits the induction of the enzyme tryptophan pyrrolase in liver cells. This enzyme, which is an oxygenase, catalyzes the first step in the metabolism of tryptophan.

There is also evidence that endotoxin interferes with the energy production which is required for cell metabolism. Adenosine triphosphate (ATP) production appears to be decreased in cells of animals poisoned by endotoxin. This effect also would result from injury to mitochondria. Takeda and co-workers reported that mice could be completely protected from the effects of a lethal quantity of salmonella endotoxin by intravenous injection of ATP if a dose of 1 mg per 20 gm of body weight was used.

Schumer and Sperling have recently proposed that we should consider shock as a disorder of the molecules of cells. They believe that the defects in the microcirculation which occur in shock cause damage to cellular function. They imply that the block at the pyruvate/coenzyme A step is due to alteration of cell metabolism, which is caused by the anoxic effect of the decreased microcirculation. Because of this block, lactic acid accumulates. The anaerobic glucose pathway is reversed, with the reaction proceeding from pyruvate to glyceraldehyde, to dihydroxyacetone to glucose-6-phosphate. Glucose (which cannot be made into glycogen since endotoxin prevents this process) leaves the cell. Amino acids, which normally enter the glycolytic pathway at the step which produces pyruvate, now leave the cell as the pathway is reversed. A similar course is taken by fatty acids which normally enter the glycolytic cycle at the pyruvate/coenzyme A step. Because of injury to the mitochondria and the decreased activity of the Krebs cycle, less energy and less than the normal amount of ATP is formed. This causes the accumulation of phosphates. Thus, the blockage in anaerobic glucose metabolism leads to the accumulation of lactic acid, phosphates, fatty acids, and amino acids in the plasma, and produces acidemia. With increasing injury to the cell (caused directly by endotoxin or by the microcirculatory deficiency) lysosomal membranes rupture, and phosphatases and hydrolases escape into the plasma.

**TREATMENT OF ENDOTOXIN SHOCK**

There is little doubt that, if endotoxin shock is permitted to go untreated for a long period, its effects may become irreversible. The best chance for successful treatment is present at the onset of shock. It is of the utmost importance that careful and continuous observation be afforded the patient who is suffering from an infection which may induce endotoxin shock. Such infections include meningococcemia and neonatal sepsis, which is very often caused by gram-negative enteric bacilli. Children with leukemia, lymphoma, and other malignant diseases who are suffering from any bacterial infection are liable to go into shock. Such patients also require special attention.

At the onset of endotoxin shock, there may be changes in the patient's mental state. There may be a loss of alertness or even brief lapses into a torpid or semi-stuporous state. Often, with the onset of shock, the pulse rate and respiratory rate rise abruptly. The blood pressure should be recorded at regular intervals, since it may drop precipitously. A fall in diastolic pressure may precede a systolic drop. It is our practice to record the blood pressure every hour during the first 8 hours after beginning treatment of patients with meningococcus.
coccic meningitis; after this period, blood pressure is taken every 3 hours for the next 24 hours.

Endotoxin shock is a multiple system disease which exerts a harmful effect on the circulation, on many organs, and on a number of metabolic processes of the patient. These deleterious effects vary with the amount of endotoxemia and with the duration of the exposure to the toxin. Furthermore, patients with septic shock are often suffering from other conditions such as coronary artery disease, malignancy, and surgical trauma. These conditions often complicate or obscure the symptoms caused by endotoxic poisoning. It is not surprising, therefore, that no single drug and no prearranged protocol will be useful for the treatment of all patients with endotoxic shock. Every patient must be treated individually, with careful consideration of all the clinical findings and of all the available laboratory data. In many instances decisions about treatment must be made almost entirely on clinical grounds. The patient may be too sick to undergo laboratory studies, or his condition may be too grave to permit the physician to wait for the results of laboratory studies before he begins therapy. Therapy should be altered promptly if laboratory data provide information which shows that such a change is needed.

With these reservations, we may outline certain principles of treatment which we believe may be useful.

1. Start treatment as soon as the diagnosis of endotoxic shock is made. To delay is to jeopardize the patient’s life. In the neonate with gram-negative bacterial sepsis or the patient with meningococcemia, the appearance of any of the clinical symptoms of shock described here warrants institution of anti-shock therapy.

2. Restore blood volume. In many instances there is no doubt that hypovolemia is present. This is the case in septic infants with diarrhea and vomiting. Children who have undergone a surgical operation and show signs of infection with gram-negative bacteria following this are often hypovolemic. Glucose and electrolyte solutions may be given as initial therapy, but blood or plasma are usually required to maintain blood volume.

3. Treat the bacterial infection which is the source of endotoxin with antibiotics.

4. Give hydrocortisone intravenously. A dose of 35 to 50 mg per kilogram is recommended. This may be given in a 10-minute period. It may be repeated at 30- to 60-minute intervals for four doses if necessary. Cortisone is recommended because, in the doses recommended here, it exerts many anti-shock effects, which include actions on blood vessels and on molecular reactions. Cortisone acts as an adrenergic blocking agent, relieving the vascular spasm caused by the abnormal action which epinephrine and norepinephrine exert in the presence of endotoxin. Cortisone exerts a favorable action on carbohydrate metabolism. It counteracts the depletion of glycogen which endotoxin causes. It decreases lactic acid formation by stimulating the pathways which lead to the eventual conversion of lactic acid into glycogen. Cortisone induces the entrance of amino acids into the pyruvate cycle and the entrance of fat into the Krebs cycle; both of these actions favor production of ATP. Cortisone has a protective action in lysosomes, preventing their rupture. Cortisone prevents kallikrein from forming kinin from kininogen. It should be noted that the concentration of corticosteroids in the plasma is not decreased in patients with endotoxemia. In fact, in some instances, the corticosteroid level is somewhat elevated. The effects of cortisone described here are obtained only with very large, “pharmacologic” doses of cortisone, which raise the plasma level far above those normally found. Many authors have advised against the use of cortisone in the presence of endotoxin-producing bacteria. This recommendation is based on the fear that a generalized Shwartzman reaction might occur if cortisone is used in these circumstances. In fact, in 1952 Thomas and Good reported that a single injection of endotoxin in cortisone-treated rabbits pro-
duced a generalized Shwartzman reaction. However, more recently (in 1967), Corrigan and co-workers[21] were unable to produce a Shwartzman reaction with endotoxin in cortisone-treated rabbits, even when they used extremely large doses of cortisone and endotoxin. We do not believe there is convincing evidence that a generalized Shwartzman reaction has been evoked in endotoxic patients treated with cortisone. We have never observed such a reaction, although we have used cortisone in the treatment of endotoxic shock since 1952.[32]

5. Vasodilators such as isoproterenol and phenoxybenzamine are recommended by some authors. Their value in endotoxin shock is not clearly established. Lillehei[26] was unable to increase the survival of dogs in endotoxin shock by treating them with phenoxybenzamine. Hydrocortisone was much more effective. We believe that the vasodilating effect which can be obtained with phenoxybenzamine and isoproterenol may be more effectively obtained with "pharmacologic" doses of cortisone.

6. Correct the metabolic acidemia if it is present. Many patients in endotoxic shock are in severe acidemia. This should be corrected by administration of bicarbonate.

7. Intravascular coagulation—when it is extensive—should be treated at once with heparin. Heparin should also be used when the clotting threatens the loss of a limb or of toes or fingers. When there is evidence of less severe intravascular clotting—such as scattered petechiae—it seems to be best at this time to look for laboratory evidence of coagulopathy before using anti-coagulation therapy. If such evidence is found in the presence of symptoms of endotoxic shock or impending shock, heparin therapy should be started. For example, if a low platelet count is found, heparin should be administered; the same is true if there is a decreased concentration of plasma fibrinogen. Abildgaard[21] recommends the use of rapidly obtained screening tests, including observation of the whole blood clot, platelet count, fibrinogen concentration by the semi-quantitative heat precipitation method, thrombin time, and partial thromboplastin time.

If a decreased value is obtained by these methods, we may assume that intravascular coagulation has occurred. However, the finding of normal values does not exclude the existence of intravascular coagulation, because, after coagulation has occurred, the clotting factors may be rapidly restored. Thus, we often must make a decision which is based on clinical judgement alone.

When heparin is used, it is given intravenously in a dose of 1 mg per kilogram of body weight every four hours. The whole blood clotting time should be kept at 20 to 30 minutes prior to each succeeding dose of heparin.[32] The laboratory screening tests referred to here should be carried out at regular intervals; and, if possible, several more time-consuming laboratory measurements should be made. These include assay of factor V and VIII. Heparin treatment should be continued until coagulation values have returned to normal or until the patient has recovered from the infection which has caused shock.

On occasion, patients under heparin treatment for intravascular clotting may have a hemorrhage from mucous membranes. When this occurs, the action of heparin may be rapidly counteracted by injection of protamine sulfate.

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ENDOTOXIN SHOCK


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