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Endotoxin shock

Donald Edwards Waltemath
University of Nebraska Medical Center

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Donald Edwards Waltemath

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INTRODUCTION: This paper is primarily concerned with the shock which frequently complicates a septicemia caused by gram negative organisms. A brief review of the literature will be presented first. This will concern itself with the incidence, causative organism, clinical picture, theories on the mechanism for the shock picture and treatment regimens. This will be followed by a discussion of the different aspects brought out in the literature review. From this a logical method of treatment will be derived.

REVIEW OF THE LITERATURE

INCIDENCE: The term endotoxin shock is used in this paper to include that shock which arises secondary to a gram negative septicemia. Shock of this nature has shown an increasing incidence since the 1940's. Martin et al (44) show that the incidence of shock was approximately 25% in the 1940's and is now approaching 33% in all gram negative septicemias. Other writers report similar incidences of shock in a proven gram negative septicemia. (48), (65)(90).

Beside the increasing incidence of endotoxin shock, there is also an increasing incidence of gram negative septicemias. McCabe (46) reports that this incidence has increased some five times since 1951.

ORGANISMS: Numerous organisms have been implicated as causing a gram negative septicemia. The following is a partial

list indicating the most frequent offenders. The numbers in parenthesis reflect the number of deaths.

TABLE I

AUTHOR	PSEUDOMONAS	PROTEUS	E. COLI	AEROBACTER	BACTEROIDES
14	8(6)	5(3)	6(5)	3(1)	
48	3(2)	6(2)	8(2)	11(6)	2(1)
75	12	14	76	24	4
TOTAL	23	25	90	38	6

In attempting to isolate the causative organism one must keep the following points in mind.

1(Draw the blood during the chill. This will increase the likelyhood of isolating the organism.

2) Incubate both aerobically and anerobically. Bacteroides and other anerobes will not be isolated if anerobic incubation is not done (49).

3) Continue incubation for at least three weeks or Bacteroides may be missed (49).

4) Sensitivity studies should be done. Importance of this will be discussed later.

PREDISPOSING FACTORS: The next point which will be brought up are factors which seem to predispose to the occurance of a gram negative septicemia. McHenry (48) noted the following pathologic entities in association with septicemia

a) Neoplasia associated with 23% of the septicemias

b) Cardiovascular disease with 17% of septicemias

c) Diabetes in 13% of septicemias

d) Pyelonephritis in 20% of the septicemias

e) Cirrhosis

f) Prior antibiotics in 18% of septicemias

g) Prior steroids in 17% of septicemias

Leukemia, included under neoplasia above, is commonly associated with septicemia. McHenry (48) lists three possible reasons for the increased incidence of septicemia with hematological disorders. This is often due to Pseudomonas species

1) Defect in gamma globulin production

2) Inadequate numbers of normal leukocytes

3) Iatrogenic ie steroids, antimetabolites, and irradiation

MORTALITY: McCabe (46) has shown that there is a marked correlation between mortality and the underlying disease process. He classified the 173 patients in his series according to underlying pathology

I Rapidly fatal disease ie leukemia

II Ultimately fatal disease ie carcinoma

III Nonfatal disease ie cholecystitis

Having done this, he noted that the highest mortality rate (91%) from a gram negative septicemia was found in patients with rapidly fatal underlying disease. Ultimately fatal underlying disease resulted in a mortality rate of 66% while the mortality from septicemia occuring in patients with non-fatal disease was 11%.

Another factor found to be associated with mortality was the presence or absence of shock. Shirley et al. (65) report an overall mortality of 37% while the mortality in the presence of shock was 56%. Spittel et al. (77) report an overall mortality of 26% in his series and Spink (70) reports a mortality of 75% in the presence of shock. From the above it can be seen that the presence of shock almost doubles the mortality.

The relationship of bacterial species to the mortality rate is not clear cut. Weil (90) related the mortality to the causitive organism and found the highest mortality in septicemias caused by Paracolon (75%). This was followed closely by E. coli 71% and Aerobacter 63%. He did not relate this to the underlying disease as discussed earlier. Hall et al. (23) noted in his series a moderate correlation of the number of organisms in the blood with the severity of shock. When there were more than 100 organisms/cc the mortality was 100%. With less than 100/cc the mortality fell to 41%. Another factor which probably affects mortality is the choice of antibiotics. This will be discussed later.

SEX AND AGE RELATED INCIDENCE: There are two fairly evident trends concerning the sex related incidence and the age groups involved. Gram negative septicemia is more common in males. Spittel et al. (75) in his series show that 66% of septicemias occur in males. Another prominent feature in this entity is that the septicemia occurs predominently after the age of 50 (46).

In females the age in which the septicemia occurs is lower than that seen in males. McCabe (46) reported that the greatest incidence in females occured between the ages 20-50 years.

PORTAL OF ENTRY: The portal of entry will be related in table II as taken from several authors. It should be noted that some authors include the biliary tract with the GI tract. Percentage numbers indicate that percent of total gram negative septicemias which the portal of entry was ascertained as in the indicated column.

TABLE II

AUTHOR	GU TRACT	GI TRACT	BILIARY TRACT	SKIN	UNKNOWN	MISC.*
L4	73%	18%			9%	
23	40%					
33	58%	16%	8%			18%
46	49%	15%		7%	22%	8%
48	77%	20%				3%
75	60%	25%			15%	
77	58%	12%	16%			

*MISC.- other portal of entry ie respiratory tract

IATROGENIC FACTORS: Iatrogenic factors are also considered by most authors to be important in initiating the septicemia. Table III is composed from the findings of several authors. Percentage figures indicate an estimation of the percent of septicemias caused by the indicated procedure.

TABLE III

AUTHOR	URETHRAL CATHETER	CYSTOSCOPY	ABDOMINAL SURGERY	IV CUTDOWN	SKIN MANIPULATION
14	69%				
33	88%				
48	91%				
75	32%	28%	66%*		
90	43%		22%	22%	13%

* The Abdominal surgery in Spittel's series (75) is broken down to biliary tract surgery 28%, appendectomy 8%, and gastric resection 5%.

CLINICAL PICTURE: By history one can usually find the portal of entry and factors, which may be iatrogenic, that were instrumental in causing the septicemia. The first sign of the bacteremia is usually a chill and spiking fever (33). This usually appears within 24 hours of the causitive mechanism (47). Spittel (75) reports this mode of onset in 67% of cases. The onset of gram negative septicemia may occur in two other ways with a fair degree of frequency. (1) Onset beginning with a temperature spike without associated chills. This is the second most frequent mode of onset, occuring in 28% of cases (75). (2) Onset beginning with shock and fever, occuring in 4% of cases (33).

Associated with the fever one will see a tachycardia. A cbc will usually reveal a leukocytosis. Weil (90) reports an incidence of leukocytosis in 86% of his cases with the average value being 18,000. A leukopenia may occur and is associated

with an increased mortality rate. (48)(75) The organisms most commonly associated with a leukopenia are Pseudomanas (48).

Shock, if it is going to appear, usually becomes manifest within 12 hours after the temperature spike (90)(69)(11). This is only an average with the shock appearing almost any time. The criteria necessary to define gram negative shock are two in number.

1) A positive blood culture during the hypotensive period (14).

2) Blood pressure less than 90/60 or a 70 mm Hg drop in the systolic pressure of a previously hypertensive person (47).

There are two typical appearances of the skin which may be associated with the shock and are of some prognostic importance.

1) The skin may be warm, dry, and give a flushed appearance. This is associated with a full bounding pulse and is considered to carry a good prognosis with it (44). Hall (23) found this to be present in 58% of his cases.

2) The skin may be cold, clammy and pale. This is associated with a thready pulse and carries a more grave prognosis (44). Hall(23) noted this in 42% of cases. The warm dry skin may progress to the cold clammy type in a manner of minutes.

There is a diarrhea frequently found in man which usually appears shortly after the onset of clinical septicemia. Martin (44) lists several possible causes of this, two of which are iatrogenic.

1) Prodroma may be related to the endotoxin

2) Chemical irritation by oral antibiotics.

3) Antibiotic induced staphlococcal enteritis

4) Underlying disease

5) Uremic enteritis

Other findings which have been noted in a significent number of cases are T and ST changes, impaired mental status, vomiting, oliguria, jaundice, Cheyne Stokes respiration, coma and cyanosis (2)(14)(90). Martin (44) gives the following list of what he considers ominous signs when found with gram negative shock.

1) Cyanosis acral parts
2) Cutis marmoralis
3) Jaundice
4) Coma
5) Cheyne Stokes resp.
6) Gallop rhythm
7) Hypothermia
8) Refractory to vasopressors
9) Dilated pupils
10) Hyporeflexia
11) Azotemia
12) Anuria

Finally a few points about the laboratory will be mentioned. Weil (90) reports an elevated BUN in 81% of his patients with gram negative shock. Martin (44) lists five possible causes for the azotemia.

1) Ischemia of the kidneys
2) Pyelonephritis
3) Prolonged vomiting
4) GI Hemorrhages
5) Nephrotoxic antibiotics

McCabe (47) reports an incidence of transient oliguria in 50% of his patients. He found this to be unrelated to shock and for this reason felt that the endotoxin has a direct effect on the kidneys. A metabolic acidosis is almost uniformly present with this syndrome

and may in part be responsible for the Cheyne Stokes respiration noted above (14)(48(90).

BIOCHEMICAL CHARACTERISTICS OF ENDOTOXIN: The endotoxin of gram negative bacteria is a phosphorus containing lipid-protein-carbohydrate complex found in the somatic portion of the bacterial cell (69). There is a considerable amount of controversy concerning which portion of the endotoxin molecule is responsible for its toxicity. According to Lewis (37) and Gilbert (18) the lipid moiety is responsible for the toxicity. Ribi (6), in some of his experimental work has come up with some findings which tend to refute this theory. He felt that if the activity were to be attributed to the lipid, one must postulate a special lipid present in minute quantities, quickly inactivated by acids. Ezzo (14) has attributed the toxicity to the protein fraction in combination with phosphorus. In general it is felt that the toxicity resides either with the protein or lipid and the antigenicity resides with the polysaccharide fraction. Gilbert (18) and Ribi (60) concluded their articles with the following possibilities concerning the fraction of the endotoxin responsible for the toxicity.

1) May be a special lipid
2) Toxicity probably resides in protein or lipid fraction
3) Toxicity may be due to a macromolecule broken down by acid hydrolysis
4) Toxicity may reside in a small compound only active when attached to an appropriate macromolecule carrier.

ACTION OF ENDOTOXIN: The following discussion is to concern some of the various actions of endotoxin as derived from experimental work on animals. A dog, when given a predetermined lethal dose of endotoxin goes through certain characteristic, reproducible phases until its death. Within minutes after the injection of the endotoxin the dog experiences a forceful bowel movement. This is followed within three minutes with hyperpnea, agitation, pruritis, vomiting, and diarrhea which continue into a phase of shivering. It is at this time that the dog is noted to develop low blood pressure. The dog develops ataxia which is present until it becomes comatose. Within 1-2 hours after the original injection the dog's vomitus becomes bloody and he is noted to have an elevated temperature. This is followed in three to five hours by a comatose state, which remains until death some eighteen hours later (18)(89)(90).

The remainder of this discussion will be primarily about the shock and possible mechanisms for its production. In considering the pathogenesis of shock one must evaluate the following possible mechanisms:

1) Decreased blood volume
2) Impaired cardiac action
3) Loss of peripheral resistance
4) Decreased venous return to the heart

The majority of this work has been done in the dog and that is what the following facts will pertain to unless specified otherwise.

I. Decreased blood volume: A decrease in circulating blood volume can come about in two different ways

1) External loss of blood due to hemorrhage

2) Loss of plasma from the vascular compartment

There is hematemesis and bloody bowel movements in the dog but this occurs after the drop in blood pressure and is not of sufficient magnitude to account for the shock. This is even more decidedly evident concerning man where there is rarely GI bleeding (39).

It is more difficult to evaluate the role of decreased plasma volume in the pathogenesis of endotoxin shock. Gilbert (18) noted the blood bolume to be within normal limits. He feels, however, that there is reason to suspect an element of decreased plasma volume in view of the vomiting, diarrhea and the possibility of increased capillary permeability. He further stated that the hematocrit is not a reliable index of this and feels that this phase should be studied further. MacClean (39) reports that there is a decreased plasma volume in dogs but questions the presence of this in man. In general it is felt that if there is a decreased plasma volume it is not of primary importance in the pathogenesis of endotoxin shock in the early phases, but may play a more important part in the late stages of shock.(87)

II. Impaired cardiac action: Weil (87), Gilbert (18), and Maxwell (43), as have many other workers, noted a profound decrease

in the cardiac output shortly after the injection of endotoxin. This could be due to impaired cardiac action or decreased venous return to the heart. Weil (87) noted that with the fall in blood pressure and decreased cardiac output the pressure in the Inferior Vena Cava remained normal. A fact which he considered to be against primary failure of the heart. Maclean (40) noted that if the venous return to the heart was maintained the immediate profound fall in the blood pressure was prevented. A factor also in favor of venous pooling as the mechanism of shock. Maxwell (43) studied oxygen consumption and work of the heart and found a less marked decrease in the oxygen consumption of the heart as compared of the ventricular work and came to the following conclusions:

1) The decreased cardiac output is primarily due to decreased venous return

2) There is some impairment of cardiac efficiency.

III. Loss of peripheral resistance: There is considerable conflict in the literature concerning the role of the total peripheral resistance in the pathogenesis of endotoxin shock. This is true in the dog where the bulk of experimental work has been done and even more true in man where very little is known concerning the status of the peripheral resistance in endotoxin shock.

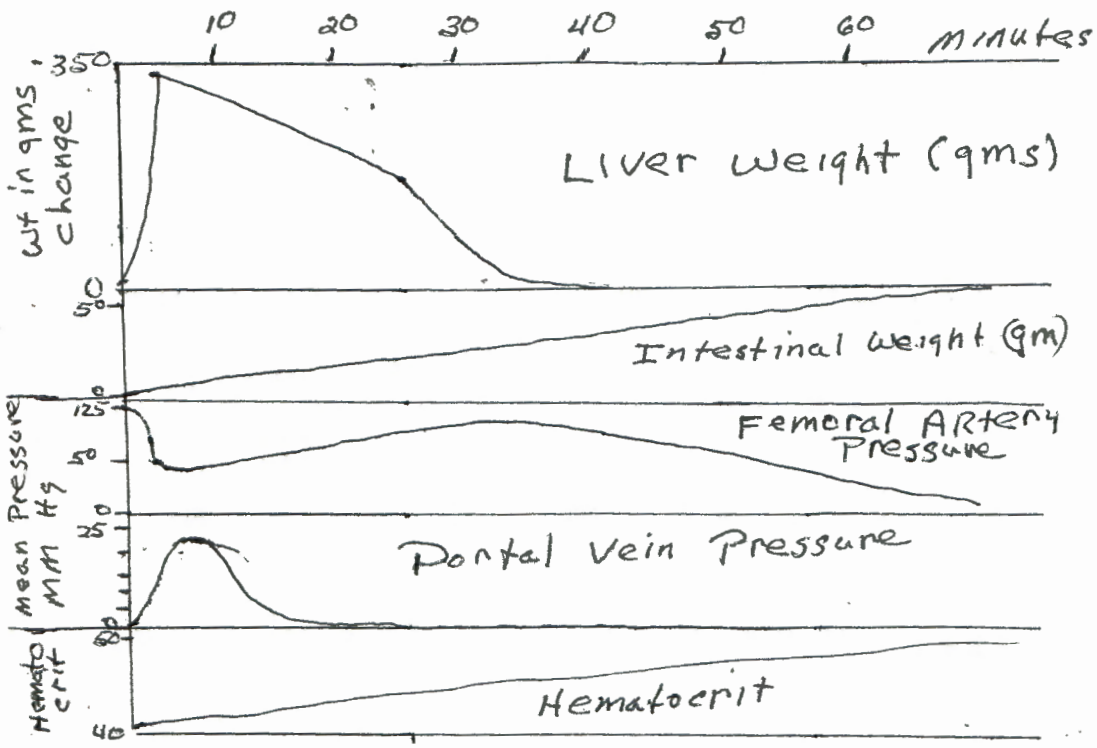
Maclean (39) noted in his work with dogs that the calculated total peripheral resistance was normal early. When the secondary fall in blood pressure occured (discussed later) there was a

decrease in total peripheral resistance. He noted in monkeys, which he felt were comparible to man, that there was a significent decrease in peripheral resistance. This has also been noted by Gilbert (20). This worker felt that in the monkey the peripheral pooling may be secondary to the decreased total peripheral resistance. Other workers, on the other hand, feel that the total peripheral resistance may be increased but not adequately to maintain the blood pressure in the face of decreased cardiac output (56)(43). Weil (87) feels that there is no change in the calculated peripheral resistance.

IV. Venous pooling: The discussion of venous pooling will be looked at from the aspect of organ systems and again the dog will be the experimental animal referred to unless designated otherwise.

1) Liver: The most marked hemodynamic changes occuring in the dog concern the blood pressure and portal vein pressure. Within one minute after the injection of a lethal dose of endotoxin one will observe a precipitous fall in the systemic blood pressure and a simultaneous increase in the portal vein pressure. These two measurements begin to return to normal within five minutes, this trend continuing over a twenty to thirty minute period (40). After this period of recovery the blood pressure again gradually falls until death of the animal. The degree of early recovery of the blood Pressure is variable but usually does not return to normal (18).

Maclean (41) drew a graph relating several variables in time. This graph is reconstructed below.



The liver is felt to play an important role in the production of endotoxin shock through one or both of the following mechanisms.

1) Trapping of large quantities of blood in the liver (40)(89).

2) The release of a vasodepressor by the liver (40)(41)(89).

Maclean (41) noted from looking at the above graph that there was a marked temporal relationship in the initial blood pressure drop, increase in portal vein pressure, and increase in liver weight. He felt the increased liver weight together with the increased portal vein pressure represented trapped blood, which resulted in a decreased venous return to the heart and a fall in blood

pressure. During this period, Gilbert (18) and Weil (87) did not find any decrease in peripheral resistance, mitigating somewhat against the presence of a vasodepressor in the blood.

Kuida (34) feels that this trapping of blood is secondary to intense hepatic vein constriction for which the dog is unique. Microscopic examination of the liver reveals the presence of smooth muscle elements within the wall of the hepatic veins of dogs (39). Many workers feel that this hepatic vein constriction is secondary to the endotoxin or a mediator "liberated" by the endotoxin (34)(39). Zweifach (91), on the other hand, feels that any stress situation in the dog will lead to hepatic vein constriction, hence this series of events are not dependent on the action of endotoxin.

The elimination of the liver from the circulation prevented the early drop in blood pressure but caused a more rapid demise of the experimental animal (40)(89). These two workers feel that this more rapid fatal course is significent and resulted because the presence of the liver is important in the removal of the endotoxin from the circulation.

There is considerable species difference when one considers the action of the liver and the production of shock. Kuida (34) reports an early marked fall in blood pressure in the cat and the rabbit. In the cat there is only a slight transient rise in the portal pressure, while the rabbit appears to be similar to the dog. The monkey and man do not show this early precipitous

drop in blood pressure suggesting that trapping of blood in the liver does not occur to any great extent in these animals (18). Maclean (39) Does report, however, the presence of hepatic vein sphincters in man.

Weil (85) reports on the comparative autopsy findings in dog and man. In the liver of the dog he noted hepatic congestion and in the human congestive hepatosplenomegally. This finding in man is not supported by Gilbert (18), who felt there was no significent hepatic congestion at autopsy.

2) Intestines: Maclean (41) shows by his graph (page 14) that the liver weight returns to normal but the weight of the intestinal loop increased progressively, independent of changes in the liver weight. He took this fact, along with the consistent finding of hemorrhagic necrosis of the intestinal wall, to indicate that the intestine is the primary site of endotoxin action. Maclean (39) also noted that this increase in weight occured after hepatectomy indicating a mechanism other than the simple backing up of blood secondary to increased portal pressure.

Several hypotheses have been advanced to explain the observations noted above

1) Increased in the resistance of the intestinal vascular bed (39).
2) Selective decrease in blood flow to the mucosae (58)(59).
3) Presence of venous sphincters in the mesenteric bed resulting in trapped blood, much as discussed earlier under the liver.

This worker feels that this fact explains the failure of vasopressors to off set endotoxin shock and the good response to adrenolytic agents (30).

Autopsy findings in the dog consist of edema, hemorrhage and ulceration of the GI tract. Intraluminal and subendothelial hyaline fibrinoid material are found in the small blood vessels of the mucosae and submucosae (85). Martin (44) reports similar findings in the intestinal tract of human autopsy cases. Gilbert (18), however, states that severe intestinal hemorrhages are not present in human autopsy cases. Gilbert (18) and Maclean (39) feel that there is little evidence for significent pooling of blood in the GI tract of man.

3) Lung: Changes in the lungs of dogs are not as dramatic as the changes occuring in the liver and GI tract. Several workers have noted an increase in the weight of the lung which occurs after the acute fall in the blood pressure. It is felt that this increase in weight is due to pooling of blood secondary to an increase in pulmonary venous pressure (19)(35)(39). Kuida (35) reports that the increase in pulmonary pressure is of the magnitude of 90-300%.

In the dog there is no evidence of pulmonary edema associated with this pooling. Kuida (35) notes that the hypotension appears first and from this reasons that there is decreased venous return thus partially offsetting the increase in pulmonary pressure. In the cat this pathologic sequence may result in death due to

pulmonary edema within five minutes after the injection of endotoxin (18). Kuida (35) notes that the pulmonary pressure in the cat increases before the fall in blood pressure. In the monkey the pulmonary artery pressure increases to a peak (258% of average) within a few minutes and returns to and remains normal within 15 minutes (34)(20).

Autopsy findings are most marked in the cat where one notes congestion and areas of hemorrhage (18). In man and dog one only finds hyaline fibrinoid material in the small branches of the pulmonary arteries (85).

4) Kidney: The effect of endotoxin, or a mediator, on the kidney is fairly well agreed to by the workers in this field. There is an increase in blood flow through the kidney of a dog after the sublethal injection of endotoxin (31)(69). The injection of a lethal dose of endotoxin results in a marked decrease in kidney weight begining within 30 seconds after the injection and progressing to a loss of 25%of the original weight by 20 minutes. (26)(18). Hinshaw (26) noted that a second injection of endotoxin at this time produced further weight loss. Spink (69) feels that this marked weight loss is due to spasm of the afferent arterioles. The kidney's weight then returns to and exceeds normal which indicates a final increase in kidney blood flow (36)(18)(39).

The question of whether or not the endotoxin has a direct action on the kidney parenchyma is not completely solved. From

studies on PAH excretion, Hinshaw (27) felt that endotoxin or a mediator has a direct action on the kidney parenchyma. Lerner (36), on the other hand, reasoned that the function impairment is primarily vascular, having found no evidence for sustained endotoxin effect on the kidney. He also noted bilateral renal necrosis, which he felt were secondary to intrarenal vascular constriction or secondary to the systemic hypotension. Other workers also feel that there is little evidence to support tubular impairment other than that secondary to vascular changes (18)(39)(69).

There has been little work with other animals. Autopsy reports of animals dieing after endotoxin shock make little mention of the appearance of the kidney. Martin (44) and Hall (23) remark on the presence of minimal renal cortical and tubular necrosis. Weil (85) in his series of autopsies makes no mention of this finding.

5) Reticulo-endothelial-system: This system has been related to the development of tolerance and also, in a superficial way, to the possible action of endotoxin in irreversible shock of hemorrhage. Lewis (37) noted that if daily sublethal doses of endotoxin were given, resistance to endotoxin developed in 7-10 days. This tolerance was noted to be nonspecific, hence not due to a specific antibody (9). Rosen (61) noted that the endotoxin was taken up by PMN and is concentrated, according to Cary (9) in the buffy coat, liver and a small amount in the lungs and s leen.

Fine (16) and Greisman (22) are of the opinion that endotoxin plays an important role in the irreversibility of hemorrhagic shock. Einheber (13) and Simeone (66) brought up several points against endotoxin in this role.

Comparison With Anaphylactic Shock: Weil (89) reports on several similarities and dissimilarities between endotoxin shock and anaphylactic shock

1) Pathologic findings very similar
2) Hemodynamic changes in the dog are similar
3) Liver glycogen and white cell changes are similar
4) Increased histamine liberation in both
5) Steroids partially affect the course of anaphylactic shock and many say it greatly alters the course of endotoxin shock.

In general there is a marked similarity between these two entities indicating a possible allergic nature to endotoxin shock.

MEDIATORS OF ENDOTOXIN ACTION: There have been several mediators proposed to help explain how the endotoxin produces the symptoms and laboratory findings summarized earlier. Ebert (11) lists several of these.

1) Adrenal cortical insufficiency
2) Direct action of the endotoxin of the central nervous system or the vascular wall.
3) Increased release of or increased reactivity to epinephrine.

4) Increased liberation of histamine.

5) Imbalance between epinephrine and histamine.

Bennet (4) in his work concerning the pathogenesis of fever felt that he had found evidence which implicated a direct action of endotoxin on the central nervous system. He contributed the lag, which occurs between the injection of endotoxin and the onset of symptoms, to that time necessary for the endotoxin to traverse into the subarachnoid space. Maclean (39) also relates of an experiment which tends to incriminate endotoxin action on the CNS. Ehdahl (12) feels that the endotoxin may work through the CNS via stimulation of the release of ACTH. Weil (89) and Spink (69) feel that the central nervous system is not important in the production of endotoxin shock.

The possibility of a direct action of endotoxin on the vascular wall has been proposed. The main evidence against this is the presence of the lag period between the injection of endotoxin and its effects.

EPINEPHRINE: There is a considerable amount of evidence which incriminates epinephrine as a major contributor to endotoxin shock. Gilbert (18) noted that the GI lesions of endotoxin shock are very similar to that following the injection of epinephrine. An increased level of catecholamines has been noted in the blood of shocked animals (25). This worker felt that epinephrine may be liberated from the adrenal medulla in increased amounts during endotoxin shock.

Zweifach (92) compared the action of epinephrine in control animals with that in animals given varying amounts of endotoxin. He found that epinephrine, when given after a lethal dose of endotoxin, produced a rapid decline in vasomotor activity resulting in the pooling of blood in veins and hypotension. Thomas (78) found that the intradermal injection of epinephrine after IV endotoxin produced hemorrhagic necrosis at the site of intradermal injection. This worker noted that sympathetic blocking agents when given prior to the endotoxin, prevented this necrosis. Animals made tolerant to endotoxin were also protected. These facts led this worker to the opinion that epinephrine was important in the production of endotoxin shock.

Thomas (79) brings up one point which seems to contradict the importance of vasoconstriction in the production of endotoxin shock. He noted that the central area about the injection site for epinephrine was often least damaged. It is at this point where one would expect the greatest damage because here is the greate t concentrations of epinephrine.

SEROTONIN: Serotonin has also been implicated in endotoxin shock. Vick (82) suggested that endotoxin interacted with serum, plasma, and platelets to release histamine or serotonin. Thomas (80) found that epinephrine plus serotonin produced an action similar to epinephrine and endotoxin on circulation of the rat mesoappendix. Another fact which this worker took to implicate serotonin was the protective action of prior treatment with the antiserotonin drug 48/80.

HISTAMINE: The agent which has been given the greatest attention, along with epinephrine, is histamine. One of the observations which has contributed to this is the similarity of endotoxin shock to anaphylactic shock as discussed earlier (89). Several workers comment on the fact that the concentration of histamine is increased in the liver and Inferior Vena Cava (18)(29)(39)(69). All of these workers except Hinshaw (29) feel that the histamine is elevated for only a few minutes following the injection of endotoxin. Hinshaw feels that that this elevation continues to rise steadily for 180 minutes.

The above facts led to the comparison of the action of histamine and endotoxin in the experimental animal. Hinshaw (28) noted that histamine caused early elevation of portal vein pressure, rapid fall in blood pressure, and eventual increase in the hind limb vascular resistance. Spink (69) noted that histamine in the monkey produced decreased peripheral resistance and an impaired response to vasopressors.

The possibility of increased histamine as a mechanism in endotoxin shock led to investigations to find why histamine was elevated. Maclean (39) and Schayer (64) found that histidine decarboxylase activity of serum was roughly proportional to the dose of endotoxin. Schayer also found that several other factors could increase histidine decarboxylase activity such as exposure to cold, serotonin, and intramuscular epinephrine. Vick (82) suggested that histamine may be derived from platelets and

Hinshaw (19) suggests hemolysis as the source of histamine. Weil (89) has also noted the elevation of serum histamine but feels that this plays little part in the pathogenesis of endotoxin shock.

In view of this incrimination of histamine it is interesting to note that the organs most involved in endotoxin shock do not share in common either a high content of histamine or any unusual susceptibility to this agent (91).

There has been a suggestion that the effect of endotoxin comes about through the imbalance between the concentrations of histamine and epinephrine. Schayer (64) proposed the following mechanism: With the injection of endotoxin epinephrine is released causing vasoconstriction. This is rapidly opposed by histamine being synthesized at an increasing rate. As epinephrine stores become depleted, the action of histamine becomes more marked. There is then vascular damage with hemorrhage and necrosis and eventially irreversible vascular collapse. This theory is also mentioned by Spink (69) and Maclean (39).

THERAPY; ANTIBIOTICS: Various authors have favorite antibiotics or combinations there of which they routinely use in the initial treatment of endotoxemia before lab studies have returned. One of the most frequently used combinations is streptomycin and a tetracycline (44)(48)(49)(70). Another frequently used combination is penicillin and chloramphenicol (2)(69). Tetracycline

in combination with chloramphenicol has also been used frequently (32)(44)(45)(47)(68)(69).

A factor which is of importance in the antibiotic chosen to treat endotoxin shock is the presence of bacterial resistance. There is conflict in the liter ture concerning the relation of in vitro resistance and clinical results. For example, Spittel (76) noted a good clinical response to oxytetracycline nd dihydrostreptomycin despite resistance displayed in vitro. He suggested that the antibiotics and a serum component were additive. McHenry (49) also noted a discrepancy between in vitro and in vivo results. The bulk of the writers, however, favor a clinical correlation with in vitro studies (23)(33)(45)(47)(90).

In discussing the role of resistance in the selection of antibiotics two charts will be presented. The first chart is taken from Sanford (63).

TABLE IV

BACTERIA	STREPTOMYCIN	CHLORAM-PHENICOL	CHLOR-TETRACYCLINE	OXYTETRA* CYCLINE
AEROBACTER	*	O	*	*
PROTEUS	*	O	*	*
E. COLI	R	O	O	O
PSEUDOMONAS	*	R	O	O
TOTAL	*	O	*	*

*--significent increase in the number of resistant strains

O--no significent increase in resistant strains

R--Preantibiotic strains were resistant

The second chart is a composit made from several authors

TABLE V

DRUG	AUTHOR	E COLI	PROTEUS	AEROBACTER	PSEUDOMONAS
Colistin	15	S	R	S	S
	32	S		S	S
Oxytetracycline	33	Highest incidence of antibacterial activity of the tetracyclines			
	84	S	33% S	50% S	
Tetracycline	33	S	S	S	R
	75	98% S	66% S	88% S	
	44	33% R	90% R	75% R	
	84				R
Chlortetracycline	33	S	S	S	R
Streptomycin	33	79% of strains are resistant			
	63	84% of strains are resistant			
	75	91% S	63% R	89% R	
	32	33% R	33% R	66% R	
	84		33% S		
Chloramphenicol	63	S	S*	S*	
	84	S	91% S	77% S	R
Polymyxin	75				80% S
	84				S*
Kanamycin	32	S	S	S	
Neomycin	32	S	33% S	50% S	

S--Majority of strains sensitive or indicated percent
R--Majority of strains resistant or indicated percent
S*--Evidence for the development of resistance

VASOPRESSORS: Greisman (22) lists several factors which one must consider when using vasopressors in the treatment of shock. Two primary locations in the vascular bed are important in the pathogenesis of shock from any cause.

1) Capillary inlet: This is primarily the precapillary sphincter which is controlled by humeral factors and local metabolites. When this mechanism fails the capillaries are flooded resulting in shock. This pooling contributes to the irreversibile shock but apparently is not the whole story. It is this precapillary sphincter and the metarteriol which are most susceptible to the action of vasopressors.

2) Caliber of arteriols: This factor is influenced by both humeral and neurogenic factors.

This author also lists several mechanisms for the capillary vascular refractoriness in septicemias.

1) Hypoxia leads to several vascular changes which may affect blood pressure. First there is an increased permeability of the endothelium resulting in the loss of plasma. This decreased blood volume results in sludging which leads to further hypoxia. As mentioned before the hematocrit is noted to raise in endotoxin shock suggesting the possibility that this mechanism may be a factor. Hypoxia also affects the action of the precapillary sphincter resulting in capillary pooling and may be a factor in irreversible shock.

2) Toxic humeral factors such as VDM (ferritin). This author feels that this is of little significence.

3) Arteriolar constriction results in increased hypoxia at at tissue levels which enhances refractoriness of the precapillary sphincter. If vasopressors have an action at this level one can see that there use may be detrimental. In fact, Brunsom (8) noted scattered areas of hepatic necrosis in gram negative bacteremia. He also feels that the degree of this is increased with the use of vaso-constrictors.

Greisman (22) comments on the following concerning the use of vasopressors. If the pressor agent increases the tone of a vascular bed already under the influence of increased tone, one might expect such agents to help early in the acute phase (increased blood flow to the head and the coronary arteries) but to be harmful over a long period. He also stated that the use of vasopressors in endotoxin shock may only mask the early manifestations by acting on portions of the vascular system not concerned directly with the decreased blood pressure.

Corday (10) noted the following relationship of the effect of shock and of vasopressor drugs on the regional circulation of various organs. He noted the perfusion of the coronaries decreased in a linear fashion with the blood pressure, and was improved with the use of vasopressors. In the liver the hepatic resistance increased and blood flow decreased with a fall in blood pressure.

With the use of vasopressors the hepatic artery blood flow increased to normal but the portal flow decreased further resulting in a net decrease in hepatic flow. This probably contributes to the hepatic necrosis mentioned above. Blood flow through the carotid arteries decreased with shock and was improved with vasopressor therapy.

The effects of vasopressors on renal blood flow is variable and appears to be related to the agent used. With shock one notes a decrease in the blood flow and an increase in vascular resistance.(10). The effect of vasopressors will be listed by the drug used and with the drugs which increase renal flow listed first.

Mephenteramine (Wyamine): This drug, according to Mills (53)(54), increases the renal plasma flow most dramatically as compared to the other agents. This was associated with an increased glomerular filtration rate GFR.

Metaraminal (Aramine) also increases glomerular filtration rate and renal blood flow RBF to a significant degree. Renal blood flow does not, however, return to normal (54) (53) (10).

Neosynephrine elevates RBF and GFR but to a lesser degree than the above two.

Levophed produced slight, if any, increase in RBF but did increase urine output significantly (53) (54). This suggests that this agent acts primarily on the afferent arteriols.

Vasoxyl causes a decrease in RBF and GFR (53) (54).

In the experimental animal the role of vasopressors is open to

wide controversy. Lillehei (38) noted that Levophed supported the blood pressure but did not improve the survival time and also found aramine to maintain the blood pressure but halved the mean survival time. This worker also administered a sublethal dose of endotoxin to dogs, primed with aramine five minutes previously, and found this proved fatal in every case. He came to the conclusion that aramine potentiated endotoxin shock. Spink (73) also noted this potentiation effect but found that aramine, when used to maintain the blood pressure of a previously shocked animal at a systolic pressure of (90 - 100), did not halve the survival time or prolong it. He also felt that the renal function was not aided, which is in contradiction to that noted above.

Weil (88), on the other hand, felt that aramine did increase the survival time when used in conjunction with steroids , concluding that judicious use of vasopressors does not promote irreversibility. He felt that aramine was useful because it prevented further pooling of blood in the splanchnic area. This increase in venous return is also confirmed by Spink (73).

A vasopressor substance which has been recently evaluated for its role in shock is angiotensin. Page (57) comments on the following hemodynamic effects of this agent. It is 2 to 10 times as potent as levophed, resulting in a decreased coronary flow, slight decreased cardiac output, decreased flow in the mesenteris artery, and a decrease in renal plasme flow. This worker felt that the vasoconstriction with angiotensin is not as severe as with nor-

epinephrine. He also noted that this increased aldosterone production which he felt was secondary to increased venous pressure. Finnerty (17) concurs with Page and adds that no skin sloughs or development of drug resistance was noted, indicating an advantage over levophed. This drug has also been used with steroids and will be discussed later.

STEROIDS: The use of steroids in endotoxin shock is also a subject open to considerable debate. It would be definitely indicated if impaired adrenal function could be demonstrated. Melby (51) noted that the secretion of cortisol in the endotoxin shocked dog was well above base line values. The magnitude of this response being approximately equal to that caused by a large dose of ACTH. He also noted that the rate of cortisol removal was impaired in the shocked animal. He concluded that the adrenal function was not disordered but felt that this did not preclude the use of steriods.

Spink (69) noted that patients having fatal bacterial shock did not have significant monphological changes in the adrenal glands. Melby (50) correlated his study in dogs mentioned above with studies in human patients. He found high levels of cortisol in moribund patients, concluding that there was suprasecretion of adrenal steriods. He noted that the half life of exogenous cortisol was greater than normal, indicating a decreased rate of destruction. He did not feel that this decreased rate of destruction was fully responsible for increased blood level of cortisone. The use of steroids in animal experiments has received considerable attention. It appears

to be fairly conclusive that the prior use of steroids in dogs (before shocked with endotoxin) has a marked protective function (18) (38) (51). It has also been shown that the administration of steroids after the development of shock in animals will prolong life and decrease the severity of GI hemorrhages (67).

The effectiveness of steroids with vasopressors has also been evaluated in the dog. Spink (73) noted that with large amounts of hydrocortisone, smaller amounts of aramine were necessary to maintain the blood pressure. This also increased the survival. This worker (74) also noted a similar response with aldosterone. Weil (88) also concurs that survival period is increased with vasopressors and steroids.

McCabe (45) noted in man that 28% of septicemia cases who were not on prior steroids developed shock and 63% of septicemia cases who had been on steroids developed shock with their gram negative infection. The mortality rate was also increased. He found a similiar correlation no matter what the underlying disease process was, and concluded that prior steroids were definitely a detriment in man.

The literature is divided on the question of the use of steroids after the development of a gram negative septicemia. Spink (70) is of the opinion that massive doses (500 - 1000mg hydrocortisone per day) are of value in the treatment of endotoxemia. Shirley (65) and Weil (90) are also of the opinion that steroids are helpful. On the other hand, Hall (23) and McCabe (85) feel that steroids

are harmful to the patient with endotoxemia and hence should not be used. Spink (69) (72) reports that the use of steroids in man does reduce the amount of vasopressors necessary. He reported the best results with aldosterone and angiotensin. The superiority of aldosterone over the other steroids has also been noted by Bein (3).

SUPPORTIVE MEASURES: Altemeier (2) and McHenry(48) report on other treatment which may be used in a supportive nature. This includes oxygen and elevation of the foot of the bed. One should be careful with depressant drugs and IV infusions. Hypothermia has received recent evaluation. Allen (1) used hypothermia in septic shock and found that the patient improved markedly when the temperature was maintained between 90 - 96 ^{o}F. He also noted these other effects of hypothermia: 1) analgesia, 2) amnesia, 3) K^{+} moves into the cell if the patient is rewarmed rapidly, and 4) no evidence of wound healing. He also commented that one should watch for cold agglutins. Allen felt that the positive effect of hypothermia was due to:

1) Retardation of bacterial metabolism and growth
2) Retardation of bacterial defense mechanism to greater degree than it affected that of man

Blair (5) also noted a beneficial effect of hypothermia. He noted that hypothermia decreased metabolic requirements, caused oxygen consumption to fall, tended to elevate refractory blood pressure (80% of cases), augmented ventilation (95% of cases), and caused arousal from coma. This worker felt that hypothermia may be indicated

in cases refractory to conventional therapy.

SYMPATHOLYTIC AGENTS: As noted earlier in this paper, epinephrine may play an important role in the production of endotoxin shock. This led several workers to evaluate the possible use of sympatholytic agents in the treatment of this entity. Nayes (55) evaluated the effectiveness of Dibenzyline and Chlorpromazine as related to the endotoxin from the various gram negative organisms. These drugs were noted to be effective only when given prior to the endotoxin. This is also agreed to by other workers (18)(38)(69). Unfortunately these drugs have not proven to be effective when given after the endotoxin (18). Nayes (55), however, has noted Chlorpromazine to afford marked protection against E coli when given two hours after the endotoxin. Weil (88) noted a decrease in survival rate when these agents were given after the endotoxin.

ANTIHISTAMINICS: The possibility of histamine laying a role in the production of endotoxin shock resulted in the investigation of antihistaminics. Gilbert (18)(19) and Hinshaw (29) noted that antihistaminics prevented the acute hypotensive reaction in dogs but did not affect the overall mortality. It appears that antihistaminics are not useful in the treatment of endotoxin shock. Gilbert (18) also fount that anti-serotonin drugs were not effective in combating endotoxin shock.

EPSILON-AMINO-CAPROIC-ACID: The use of Epsilon-Amino-Caproic acid (EACA) in the treatment of endotoxin shock in dogs has been

evaluated by Spink (71). This came about by the possibility of endotoxin activating the Plasmogen-Plasmin system resulting in hypercoagulability. EACA is a potent inhibitor of Plasminogen activation. Spink found that pretreatment with this agent increased the survival of dogs, in fact, showing some hypertensive effect. This drug also proved effective when given after endotoxin. At present it is to premature to consider the use of this drug in man until further evaluation is done.

HYDRALAZINE: Hydralazine has been recently evaluated by Vick (85) because of its ability to increase renal plasma flow. He found that when this drug was used alone there was no beneficial effect but when used in conjunction with Aramine and cortisone an increase in survival rate was observed. This increase was from 60% survival without the use of the drug to 80% survival with the drug. The use of this drug also resulted in an increase in urine volume.

DISCUSSION

As has been noted previously in this paper, there is an increase in the frequency of gram negative septicemias. There are several possible reasons for this:

1) Gram positive organisms are being suppressed allowing for the overgrowth of gram negative bacteria (90).
2) There has been evidence of the emergence of resistant gram negative strains (90).

3) There is an increased number of patients with disabling diseases.

4) There is an increased awareness of this entity leading to a greater frequency to diagnosis.

Concerning the first reason, McCabe (46) found in his series that 50% of the patients had been on prophylactic antibiotics at the onset of the gram negative septicemia. The most common antibiotics being penicillin alone or in combination with streptomycin. This fact brings up the important point of the value of prophylactic antibiotic therapy. The possibility of this contibuting to an increasing incidence of gram negative septicemia must be given very careful consideration when one contemplates prophylactic therapy. The evidence on the emergence of resistant gram negative strains will be taken up later in this report.

The life expectancy of the population in general has increased markedly during the last two decades partly as the result of modern medicine and the advent of antibiotics. Associated with this progress,the population must contend with new illnesses. Among these illnesses are an increased incidence of cardiovascular disease, carcinoma, and other chronically diasabling entities. This provides fertile grounds for the development of infectious processes including gram negative septicemias. This accounts in part for the increased incidence as noted above. Concerning the fourth reason listed above, this is self explanatory and will not be discussed further.

Implicated organisms are revealed with their relative frequency in Table I (page 2). One is at first impressed with the relative frequency of E coli as a cause of septicemia in Spittel's series as compared with the other two. There is one factor which may account for this. Spittel's (75) series begins in the early 1940's and covers fifteen years, while the other two are over a much shorter time period. Possibly the septicemia due to E coli occured predominently in the earlier years of Spittel's series. This may, in turn, provide presumptive evidence of the role of "prophylactic" antibiotics in selecting the organism which will ultimately cause the septicemia. Further support to this theory may be found in the various sensitivity of gram negative organisms to the presently used antibiotics. Work by Sanford (63) and Martin (44) reveals that E coli has remained relatively sensitive to the various antibiotics while the other organisms show various degrees of increasing resistance.

Thus accounting for the frequencies reported by Spittel (75), one can see that Pseudomonas, Proteus, E coli, and Aerobacter all have approximately the same frequency in gram negative septecemias, although E coli is still probably the leading offender. Other organisms implicated are Bacteriodes, Alcalegenes, Paracolon, Salmonella and Neisseria. In trying to isolate the organism one should keep in mind the suggestions of McHenry (49) noted earlier in this paper.

The portal of entry and iatrogenic factors which result in a

gram negative septicemia are related in Table II and III (page 5 and page 6). The GU tract is the most frequent portal of entry as agreed by all authors. The reported incidence varied from 40% to 77% with the average probably being somewhere around 50%. The most frequent offender in this group was found to be catherization and is probably related to the frequency with which this procedure is carried out. It is especially worth noting that in several of the reported series this supposedly benign procedure resulted in more than one half of the cases of septicemia. One should realize from this that it is not a benign procedure and should be undertaken only with definite indications.

Spittel (75) found cystoscopy to be the portal in eighteen patients out of 137. The organism involved being E coli, Proteus, Aerobacter, and Pseudomonas. Transurethral resection is also a frequent offender with E coli being the predominant organism.

The GI tract is the second most frequent portal of entry with incidences varing from 12% to 25% (average about 20%) depending upon the investigator. Biliary tract surgery is the greatest offender in this group. E coli and aerobacter are probably the most common organisms noted. Other inciting factors were surgery on the bowel, gastrectomy, paracentesis, peritonitis and appendectomy.

In septicemia arising from skin infection, pseudomonas frequently is implicated. This is especially true if the patient has been on systemic antibioties.

Mortality is related to underlying pathology, presence or

absence of shock, and causitive organism. Mortality can most easily be related to the underlying pathology, with the mortality rate increasing as the severity of the underlying disease. The presence of shock also appears to effect the mortality in that mortality rate is almost doubled. Several authors attempted to relate mortality to the causitive organism. There is little correlation between their findings. It should be noted that these papers did not relate mortality to underlying disease.

The action of endotoxin has been extensively investigated in the experimental animal. Unfortunately the experimental animal most frequently used is the dog. This leads to a considerable degree of difficulty in relating the findings in this animal to what happens in man because the endotoxin action appears to vary greatly between these two species. Very little work has been done with the monkey, an animal which appears to resemble man as far as the action of endotoxin is concerned.

If one compares the clinical course in man with that seen in the dog, considerable difference is noted. One contributing factor to this difference is the presence of the organism in man whereas only the endotoxin is present in the dog. This in itself adds an important variable to septicemia in man. Another important variable lies in the fact that the dog is faced with a sudden lethal challenge, while in man this challenge develops over a period of hours.

The onset of symptoms in the dog is predominately gastrointestinal in origin which is followed shortly by a temperature

spike and chills. In man it is usually the later which heralds the onset of the septicemia. The endotoxin has a characteristic action on the vascular beds of the liver and mesentery of the dog, which if it occurs in man it is much less marked. This difference probably accounts for the bloody vomitus and diarrhea found in dogs and usually not found in man. This action on the vasculature will be discussed later.

Four mechanisms for the production of shock were reviewed earlier from the literature. The first mechanism considered was shock secondary to a decrease in blood volume. Blood loss was evaluated and discarded as a possible mechanism by the workers in this field. A decrease in plasma volume was also considered. It was felt that this may assume importance in the later stages of shock but was not of primary importance in its pathogenesis. Cardiac action was also evaluated and discarded as not being of primary importance.

The status of peripheral resistance assumes importance when one considers the use of vasopressor agents in therapy. If the shock were due to a decreased total peripheral resistance, vasopressors would seem to be indicated. If, on the other hand, the shock were due to a decreased cardiac output with compensatory vasoconstriction, the use of vasopressors may prove harmful even in the face of a falling blood pressure.

There is one point which I feel needs mentioning here. In experiments with dogs the first change following the injection

of endotoxin is a marked increase in portal pressure with pooling of blood in the splanchnic area. This is associated with a profound early drop in blood pressure which lasts about ½ hour. Following this there is a secondary prolonged drop in blood pressure which is more camparible to that seen in man. Therefore if any relationship of total peripheral resistance changes in dogs to man is made, one must consider these differences. For example, Weil (87) made his study only during the first half hour of shock and hence his findings may bear little resemblance to that found in man.

The literature was well divided on the subject of peripheral resistance changes. This is probably a manifestation of the difficulty in measuring this variable. This is complicated by the multitude of methods used to evaluate peripheral resistance and the lack of standardization of these methods. More work is required on peripheral resistance in dogs during the later stages of shock and in other shocked animals before any valid statement can be made concerning its role in the production of endotoxin shock.

The aspect of venous pooling was reviewed by order of organ systems involved. The liver was discussed first and several conclusions were drawn:

1) There is considerable species difference in the action of endotoxin, making it difficult to apply the findings in any one species to man.

2) In the dog, the early blood pressure drop appears to be related to trapping of blood in the liver. This probably being related to the hepatic venous sphincters. This extensive pooling does not appear to play a major role in man.

3) The liver appears to be important in the removal of endotoxin. This is probably also true in man as evidenced by the increased mortality in patients with liver disease.

4) It is hard to make any statement concerning the role of the liver in the production of the shock by autopsy findings. First, congestion of the liver is a frequent finding at autopsy, so its relative importance here is hard to access. Second, the autopsy is performed some hours after the time which the liver is supposedly ascerting its effect.

There appears to be ample evidence that the GI tract plays a very real and important role in the pathogenesis of endotoxin shock in the dog. The mechanism for this must remain undetermined at the present time. There are two facts which are pretty well agreed to by the workers in this field: 1) Gain in weight of the intestine and 2) hemorrhage and necrosis of the mucosae and submucosae. The presence of vein sphincters will explain the gain in weight, but the slow progression of this weight gain is not compatible with this theory. If the gain were due to this sphincter action, one would expect a much more rapid weight gain as seen in the liver.

A more appealing theory to me is that the weight gain is due to plasma loss through damaged endothelium and the hemorrhage noted is secondary to the same process. This damage could arise in one of two ways.

1) Direct action of the endotoxin or a mediator on the endothelium

2) Ischemia secondary to selective vasoconstriction. Evidence indicates that this vasoconstriction involves arteries to the mucosae and submucosae.

A possible corollary to this second mechanism would be that the use of vasopressors would enhance the process leading to an increased mortality.

How all of this fits into the human picture of endotoxin shock is difficult to establish. Certainly by clinical criteria, the GI tract is not as severely effected in man as in dogs. If pooling does occur in the GI tract of man it is to a relatively less degree than that in dogs and cannot be used alone to account for the shock picture.

The role of the lung in venous pooling assumes greatest importance in the cat where death from pulmonary edema is a frequent occurence. The Cheyne Stokes respirations found in man is probably not related to changes in lung vasculature and may, in part, be related to the concurrent metabolic acidosis.

It is evident that pooling of blood is of great importance in the production of shock in the experimental animal , with the

location of this pooled blood varying from species to species. The relationship of pooled blood in the endotoxin shock of man is not as readily apparent. Pooling probably plays an important part in human endotoxin shock but the distribution of the blood is not primarily in one organ system but more likely spread out more diffusely.

It has been shown that tolerance develops to endotoxin which is non-specific in nature. This may play a role in the mortality rate in the endotoxemia of man. It has been noted by several workers that there is a low mortality in cases in which the portal of entry is the GU tract (46). This may be due to the development of tolerance secondary to seeding of the blood stream with gram negative organism from the urinary tract.

An abundance of confusing literature has been published concerning the action of endotoxin in causing the shock-like picture. A direct action on the central nervous system has been evaluated as the cause of septic shock, but most authors consider other mechanisms to be more important. Epinephrine has been extensively evaluated and does appear to play a role in the production of endotoxin shock. The mechanism by which epinephrine acts must remain open to question at present, although it does enhance venous pooling. Histamine has also been extensively evaluated and many authors consider it of primary importance.

As is the pathologic process in man, the part these various mediators play in endotoxin shock is presently more a matter of speculation than proven fact. Most of the work has been done

with epinephrine and histamine and hence there is more written evidence concerning their part. It is quite possible that some of the lesser investigated agents or agents yet to be discovered will be of more importance. At any rate, this entity probably results from the complicated interaction of several factors, among which epinephrine and/or histamine may be involved.

The first consideration in therapy is the antibiotic or combination of antibiotics which is most likely to be effective. In the beginning the choice is emperic of necessity because one cannot afford to wait for pertinent lab results. In making this selection one must consider the probable portal of entry, the most likely causitive organism, the antibiotics most likely to be effective, possible deleterious effects of the selected antibiotic, and emergence of resistant organisms.

The portal of entry is to be considered because it may be helpful in deciding which is the most likely organism. This factor was discussed earlier in this paper. The GUtract is the most frequent portal of entry with the most likely organism being E coli, Aerobacter, and Proteus. The most likely organism from the second common portal, the GI tract, are E coli and Aerobacter. Pseudomonas is frequently implicated when the portal of entry is the skin. Other findings which tend to implicate Pseudomonas are thrombocytopenia, leukopenia, or icthma gangrenosum. Prophylactic antibiotic therapy frequently result in septicemia caused by Pseudomonas, Aerobacter and Paracolon.

In looking at Chart IV (page 25) and Chart V (page 26) there is one fact which stands out quite prominently. Streptomycin has not proven very effective in vitro in combating the gram negative organisms. There is also evidence th t these organisms are becoming even more resistant to this drug. This is a very good indication that Streptomycin does not have the broad spectrum activity it i commonly thought to have. From this the following assumptions can be made.

1) The penicillin and streptomycin, often ordered post-operatively as prophylaxis against infection, is quite possibly in error. This may contribute to post-operative septicemia caused by gram negative organisms.

2) The use of emperic Streptomycin in endotoxemia before culture results have been reported is not well founded by in vitro studies and should not be relied on.

3) Probably the only use of Streptomycin in endotoxin shock would be laboratory evidence of a sensitive organism in a patient who has not responded to other therapy.

Colistin is a drug which has been suggested in recent years as having value in the treatment of gram negative septicemias. From Chart V one notes its marked similarity to Polymyxin B especially in combating Pseudomonas infections. The possibility of increased number of resistant Pseudomonas strains to Polymyxin B may portend an increased importance of this drug in treating septicemias due to this organism. There are several drawbacks to the

use of this drug in the initial treatment of gram negative septicemias

1) Expensive antibiotic (15)
2) Nephrotoxicity and paresthesias have been reported.
3) Fekety (15) noted the possibility of antagonism of this drug with the bacteriostatic agents. An important drawback if one is going to consider the use of the tetracyclines.
4) Fekety (15) noted the development of a few resistant strains with treatment. In vitro there was facultative one step changes, which were unstable and quickly reverted back.
5) The one notable exception to its broad spectrum activity is the resistance of Proteus species. This assumes even more importance when one considers that this organism is a frequent offender in septicemias due to gram negative organisms. For this reason Colistin should not be used in the initial therapy unless used in combination with an antibiotic effective against Proteus.

The tetracyclines have been widely used for their broad spectrum activity. As noted from Chart IV (page 25), there is evidence of the development of resistance in certain gram negative strains, namely Proteus and Aerobacter. Evidence for this can also be seen in Chart V (page 26). The incidence of resistant Aerobacter strains to tetracyclines was approximately 21% in Spittel's series and was 75% in Martin's series. This is a significent difference. The change in relation to Proteus is small, 66% as compared with

88% and probably is not significent. A similar comparison cannot be made with the other tetracyclines from Chart V. Koch (33), however, reports cross resistance among the tetracycline group of drugs. E coli has remained essentially sensitive to the tetracyclines.

The tetracycline drugs used alone would appear to be effective against E coli but are relatively unlikely to be effective against Proteus and Aerobacter. Hence this group of drugs should not be used alone to initiate therapy against gram negative septicemias, but should be used in combination with another antibiotic. The one area in which these drugs may be the antibiotic of choice is in connection with infection with Bacteroides.

The next drug to be considered in the initial treatment of gram negative septicemia is Chloramphenicol. From Chart IV it can be seen that Chloramphenicol has remained effective in combating gram negative bacteria. From Chart V it can be seen that Wallbren (83) considers this drug the most effective antibiotic against Proteus organisms. He also found that this drug, in combination with oxytetracycline, was effective against 91% of Proteus strains tested. It can also be noted from Chart V that chloramphenicol is not effective against Pseudomonas which is a drawback to the use of the antibiotic in the initial treatment.

The toxicity of Chloramphenicol can also be brought up in the argument against its use in therapy. Among these toxicity symptoms are nausea, vomiting and diarrhea. Most of these symptoms can be

explained by alternation in the gut flora. The important toxic manifestation of Chloramphenicol is depression of the bone marrow resulting in blood dyscrasias such as aplastic anemia and agranulocytosis. The incidence of this type of toxicity is low, probably occuring in no more than 1 out of 200,000 to 250,000 patients (93). Although infrequent, The seriousness of this toxic manifestation dictates that this drug should not be used to treat minor infections. Gram negative bacteremia is certainly not a minor infection, and in view of the high mortality this drug has a very real place in therapy.

To what extent should this drug be used?

1) Initial therapy in gram negative septicemias associated with shock: This drug has proven effective against the majority of gram negative organisms implicated in causing septicemia.
2) Gram negative septicemia without shock: The drug should probably be used here also. The mortality rate still approaches 25%.
3) For an added safety factor this drug should be used in combination with another effective antibiotic. In looking at Chart V it appears that either a tetracycline or Kanamycin would be the best choice. The bulk of the literature favor a tetracycline in this role. If Pseudomonas were expected, Chloramphenicol should be used with Colistin or Polymyxin B. Combination with Neomycin has also been recommended (84).

This drug is metabolized in the body and does not depend on the

on the renal function for excretion. Therefore renal failure is not a contraindication to its use.

The next drug for consideration is Polymyxin B. Chart V reveals this drug to be effective only against Pseudomonas aerugenosa and also indicates that possibly this drug is becoming less effective against this organism. McHenry (48) lists three situations in which Polymyxin B may be indicated

1) Clinical or microscopic evidence of Pseudomonas
2) Inadequate emperic therapy after 48 hours
3) Poor clinical response to organism shown to be sensitive to Polymyxin B.

In using this drug care should be taken for possible renal toxicity, paresthesias, and cerebellar ataxia.

Kanamycin has a wide range of antibacterial action. Katz (32) and McHenry (48) suggest that serious consideration of this drug is indicated if the initial therapy should prove ineffective. This worker considers this drug to be indicated if staphlococcal septicemia is suspected. In using this drug one should beware of its ototoxic activity. I feel that this drug does have definite use in gram negative septicemia, probably being indicated if the initial therapy appears to fail.

Neomycin is another antibiotic to be considered. According to Chart V it is of less effectiveness against Proteus and Aerobacter than is Chloramphenicol and of about equal effectiveness when compared to the tetracyclines. Neomycin concentration may

become elevated in the face of renal failure because the urinary tract is the principal excretory route. Neomycin is ototoxic and nephrotoxic, indicating that this drug should not be selected over tetracycline unless lab studies reveal organisms sensitive to this drug.

Antibiotic therapy must by necessity be instigated at least 48 hours before sensitivity studies have been reported. I tried to show why I feel Chloramphenicol and a tetracycline should be used initially. Possible exceptions to this would include

1) Suspect Pseudomonas--Use Polymyxin B or Colistin in place of the tetracycline
2) Suspect staphlococcal infection--Use penicillin or Kanamycin

Martin (44) recommends that if there is not clinical improvement after 12 hours one should change antibiotic therapy. The drug to be substituted again must of necessity be emperic. Probably Polymyxin B or Colistin should be used in place of the tetracycline because the initial therapy is known not to be effective against Pseudomonas, a commonly implicated organism.

When susceptibility tests return, two possibilities exist.

1) If adequate clinical response is occuring the therapy should not be changed despite the lab results (48).
2) If response is poor one should try to derive an acceptible combination of drugs as determined by the lab results.

Antibiotic therapy should be continued until afebrile for at least 72 hours and three successive blood cultures are negative.

The value of vasopressors in man is even more controversial than its use in animals. One important point should be made however; their use is generally accepted by the medical profession, hence, vasopressors should at present be used in endotoxin shock if for no other reason than medical legal purposes. It can be expected that the use will continue until very definite and indisputible evidence is produced to show that they are valueless. In dogs the evidence is not very impressive that vasopressors are useful. It is hard to correlate effectiveness with mortality because as mentioned earlier the underlying pathology appears to be the main determinant of final results. This is compounded by the absence of control groups, as a large enough number have not been treated without vasopressors.

Vasopressors should be used only to the extent that the systolic pressure is maintained at not over 100-110. It is felt by most workers that if the systolic pressure is maintained higher than this there are definitely detrimental effects (44)(65). Most workers also agree that Aramine and Levophed are the agents of choice (44)(90). Angiotensin is recieving increasing acclaim recently.

The known actions of vasopressors is helpful in determining which agent should be used. These agents seem to increase coronary blood flow and carotid flow, which is probably the one clear cut indication for their use in endotoxin shock. Angiotensin, however, is reported to decrease coronary flow, a possible contraindication to its use.

The decrease in urinary flow commonly noted with endotoxin shock suggests that renal blood flow should be protected if possible. As noted before, Vasoxyl decreases renal blood flow indicating a contraindication to its use. Wyamine is the most effective drug in increasing the renal blood flow. This drug, however, does not appear to be sufficiently potent to be effective in endotoxin shock (21). For this reason this drug is not frequently resorted to.

Aramine is the second most effective drug in increasing renal blood flow. This drug is also mentioned by several workers to be quite effective in elevating blood pressure due to increased venous return. Its prolonged action, absence of local injury, and different possible routes of administration are attractive. This drug probably warrants early trial innshock due to gram negative septicemia.

Levophed is the most potent vasopressor in present extensive use. This drug produces vasoconstriction of arterial, capillary, and venous vessels. This drug should be reserved for treatment in cases refractory to Aramine.

Angiotensin is still to be evaluated. The fact that it decreased renal blood flow and coronary artery flow may be taken at present to be a relative contradiction to its use. Greco (21), however, had good results with this agent in treating endotoxin shock. This agent produced an elevation of blood pressure where Aramine had failed. He did not make a similar comparison with Levophed

The efficiency with which these agents increase blood pressure must be taken in light of Greisman's (22) statement that an improvement of the blood pressure is not necessarily synonymus with therapeutic benefit. The agents to be used appear to be Aramine first followed by Levophed. Angiotensin may become more important in the future, possibly in combination with a steroid.

The use of steroids in gram negative septicemia is open to considerable controversy. It appears to be well established that adrenal function function is not impaired and hence the use of steroids cannot be rationalized on this basis. The dramatic results in dogs would, on the surface, appear to be ample reason for the use of steroids in man but one must remember that the live organism is present in man,,a very important difference. McCabe's (45) finding that septicemias in patients on prior steroids carried an increased mortality rate is good evidence against their use in man. The one place where steroids may be indicated in this entity is in endotoxin shock refractory to vasopressors. The use of these agents may maintain coronary and cerebral perfusion when used in conjunction with a vasopressor. Aldosterone may be the steroid of choice.

Sympatholytic agents, antihistaminics, serotonin antagonists and hydralazine are not indicated at present and should not be used. Epsilon-Amino-Caproic acid is incompletly evaluated at present and hence it should not be used. Hypothermia appears to be very effective and may play a real role in the treatment of gram

negative septicemia with shock. This method of treatment may replace steroids in refractory cases.

SUMMARY

This paper was intended to be a brief review of the literature on the clinical picture and treatment of gram negative septicemia with shock. At the outset it was noted that there has been a marked increase in the incidence of septicemia in recent years.

A combination of several articles revealed that Pseudomonas, Proteus, E coli and Aerobacter were the main offenders in causing the septicemias. The possibility of "prophylactic antibiotic therapy" as a cause of the increasing incidence was discussed. Neoplasia was found to be the most frequent underlying disease.

The mortality was found to be related to several factors such severity of the underlying disease and presence or absence of shock. Several authors attempted to relate mortality to the organism involved but there was little correlation between their reports. The GU tract was found to be the most frequent portal of entry followed by the GI tract.

The clinical story was next discussed and it was found that a chill and temperature spike was the most common hearldry of the onset of the septicemia. This was compared to that seen in dogs with the resulting conclusion that there was considerable difference between the two.

The action of the endotoxin on the various organ systems of the experimental animal was discussed. There was marked species difference found although pooling of blood appeared to be a frequent common denominator. This was most marked in the dog and less so in the monkey and presumably in man. No definite conclusion could be made concerning the importance of pooling of blood and total peripheral resistance in the cause of shock.

Confusion reigned supreme when we entered upon the discussion of possible mediators of the endotoxin action. There were approximately as many theories as authors. Epinephrine and histamine did, however, appear to play an important role.

The mainstay of treatment is antibiotics. Although there is some differences of opinion regarding the value of in vitro studies, most workers felt that in vitro correlated fairly well with in vivo results. From this a case was made for the use of Chloramphenicol and a tetracycline in the initial treatment. Several suggestions were then given for the continuation of antibiotic therapy.

Vasopressors were next discussed and it was found that it was hard to prove a definite indication for their use. Maintainance of coronary and carotid blood flow appeared to be the only definite indication for their use. Aramine, Levophed and possibly Angiotensin were suggested for use.

The use of steroids was also controversial. Large series revealed the possible detrimental effects of these agents. There use now is possibly a hangover from the steroid as a panacea era.

It was concluded that their use may be indicated in refractory cases where all other measures have failed.

Supportive therapy was discussed and hypothermia was found to be possibly of great help in the future. Other agents which have been suggested in treatment were discussed and set aside for the present.

In all the mortality cannot be expected to be lowered to any significant degree until very real advances are made in the action of the endotoxin - why it acts, how it acts, and where it acts. When these facts are discovered, better theraputic measures will be found resulting in a more optimistic outlook.

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