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Bacterial factor in secondary shock

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(Appendix I)

THE BACTERIAL FACTOR IN SECONDARY SHOCK

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(Appendix II)

OUTLINE

BACTERIAL FACTORS IN SECONDARY SHOCK

I. Introduction

This thesis is concerned with shock where bacterial infection is a factor. This will include of course shock due to sepsis primarily; shock where bacterial invasion is secondary, such as trauma or burns; it will also include consideration of a bacterial factor in protracted secondary shock or so called "Irreversible Shock".

Although some would like to do away with the term "shock" and replace these conditions with terms explaining the etiological cause,[1] "shock" is a frequently used clinical term and regardless of cause appears to be characterized by hypotension,* tachycardia,* cold moist skin and pale cyanotic mucous membranes. Other subjective signs such as thirst, restlessness, etc., may or may not be present.[2] This condition has a variety of etiological factors such as acute hemorrhage, trauma, burns, or sepsis. Fundamentally however, there is a "disparity between the circulating blood volume and the size of the vascular bed".[3] In acute hemorrhages, this is due to blood loss directly, and failure of compensatory mechanisms such as tachycardia,

*Birchwall, R. Amer. J. Surg. 76: 51-57 1948
Described a few cases of war shock where tachycardia (HR>90) or hypotension (BP<100) were not present.

vasoconstriction-to maintain a normal blood pressure, etc. In other conditions there may not be an actual fluid volume loss. The importance of bacteria in shock has been recognized for many years. Laenec[4] in 1831 described the weak heart sounds of failing circulation in acute febrile illness. The pathologic physiology of shock of acute infection was adequately explained in 1907 by Janeway[5] who attributed it to failure of peripheral circulation with pooling of blood in the capilaries. Our modern concepts of shock, however, stem from Cannon and his excellent treatise on traumatic shock in 1923.[6] He speculated at that time that secondary shock may be produced by liberation of a toxic material in the body. The nature of this toxic material was not defined. This has provided the groundwork for speculation and research which have produced a better understanding and new fields of etiology as well as treatment in medicine today.

I shall attempt to present the most definite and accepted role of bacteria in shock first. The more problematical and controversial we shall save till last.

With this in mind-let us turn to the role of sepsis in the etiology of traumatic shock.

II Sepsis Shock

There are numberous reports in the literature of shock due primarily to sepsis. Meningococcemia, pneumonia, tetanus, gas gangrene, staph sepsis, and gram negative sepsis are a few of the offenders. There appeared to be no decrease in plasma volume. Venous pressure was normal and elevation of the foot of the bed did not improve circulation. Transfusion with blood or glucose was inadequate treatment. Improvement was found only with correction of the infection.[7,8,9,19,11] This was accomplished through antibiotics, antitoxins and general supportive measures. The actual pathological physiology in this condition is known in several of the conditions such as meningococcemia and gas gangrene. Tetanus and botulism toxins appear to act on the myoneural junctions and cause paralysis of the nerve endings. Cl. welchii produces a lecithinase which lyses tissue. Diptheria toxin blocks synthesis of cytochrome enzyme formation. In meningococcemia, part of the brain is swollen and purulent exudate may be found-

along the cerebiospinal fluid pathway. Hemorrhage into the adrenal (Waterhouse-Fridericksen syndrome) may be responsible for the peripheral vascular collapse. In other infections, there apparently is a widespread, generalized effect with no particular organs grossly abnormal when seen at autopsy.[12] Several things appear to happen almost universally- hypoxia, vasomotor collapse with capillary dilation, and possibly anemia due to hemolysis by toxins, cardiac impairment by toxic effect on the heart.[13] The liver is often edematous. Most of these conditions are commonly seen in all types of secondary shock.

The problem of sepsis shock then resolves primarily into recognition and adequate anti-bacterial measures. Fluid therapy should be an adjunct as with any condition where dehydration is a factor, but it is important to avoid overhydration. Pulmonary edema can result from over loading the already adequate blood volume.

Altemeir has shown in dog experiments that the absorption of antibiotics is retarded slightly but not prevented in shock. His results were for peak blood levels. Results of a study of 46 dogs:[14]

*Mac Leod, C. M. & Pappenheimer, A. M. Properties of Bacteria which Enable Them to Cause Disease. Bact. and Mycotic Inf. of Man. Lippincott 1952

		Shock	Control
I.M.	Penicillin	1-2 h.	½ h.
Oral	Penicillin	½-1 h.	½ h.
Oral	Aureomycin	3-5 h.	2-3 h.
I.M.	Aureomycin	2-4 h.	2-4 h.
I.V.	Aureomycin	½-1 h.	½-1 h.

It was noted that in shock the peak level was maintained somewhat longer. Penicillin was absorbed quicker in both the oral and the intramuscular routes. Of course-peak levels of antibiotics do not insure reversal of sepsis shock. We are reminded of the ineffectiveness of penicillin in advanced diptheria. It is often the toxic products (toxins) which must be combated as well as the bacteria themselves. It was shown experimentally in dogs, that heavily infected muscle fluids injected into recipient animals produced profound shock. Centrifugation and injection of organisms produced only fever. Supernant fluid however was equally as toxic as the original producing prodound shock. Antitoxin given before-no shock resulted.[15]

Thus we have at least the ground work for an understanding of bacterial shock and possibly some hints as to its proper treatment.

III Secondary Sepsis Producing Shock

Secondary infection of burns is a dreaded complication. Severe trauma with gross bacterial contamination may produce shock also. Several of the series of this sort of thing came from war medicine. In a study of shock caused by extremity wounds in 1,156 casualities in World War II-in 65 patients or approximately 6%, either gas gangrene or an unknown factor, presumed to be infection, were the cause. Most (75%) of this "unknown" group had received injury from a mine explosion with gross contamination. There was a 20% mortality in this group although operation with debridement or amputation usually resulted in improvement and reversal from the shock condition.[16] In war medicine, the problem of shock has most entirely resolved into replacement of blood loss. A remarkable response to blood therapy in battle wounds has been shown.[17,18] It is interesting to note that low titer O positive blood without cross-matching was used almost exclusively. This was necessitated because of inadequate facilities for cross matching, but had the advantage that blood

could be given very rapidly without the delay of cross-matching. The incidence of blood reactions also in the service was almost nil. It must be remembered however-that even if the problem of shock in service casuality medicine may be nearly completely solved by blood-civilian medicine presents an entirely different situation. The fighting man is at the optimal age and top physical condition. Defense mechanisms are at their peak. Practically without exception-prior to injury these men had no complicating factors such as cachexia, coexistant disease or dehydration. This is a sharp contrast to civilian medicine with patients in the older age group, complication of factors rather than one, and depletion of blood proteins, making the problem in civilian practice much more complex.

One other factor that should be considered is transfusion of bacterial contaminated blood. Braude[19] showed in a series that 2.2% of refrigerated blood at the University of Michigan cultured bacteria. It was shown that psychrophilic (4-8°C) and mesophilic (37°C) bacteria may be a factor in bacterial contamination of blood.

Several of the organisms reported associated with severe transfusion reactions are:

E. coli	3
B. coli aerogenoides	4
E. Freundi	2
Paracolon aerogenoides	2
Alcaligenes fecalis	1
Achrombacter sp.	1
Pseudomonos sp.	5
Intermediate coliform	1
	19

This investigator felt that injection of 10 mg/pint of broad spectrum antibiotic would probably eliminate the possibility of reaction. This ignores the problem of bacterial toxins and breakdown products in blood. Experimental studies showed that antibioties appeared to adequately prevent reactions however. Examination of a blood smear for bacteria or culture also might be worthwhile procedures. Laboratory precautions and sterile technique would minimize the possibility of reactions. War medicine concluded that the evidence of reaction was so small that the above antibiotic measures, etc., probably are unnecessary.*

*Crosby, W.H.: The Safety of Blood Transfusions in the Treatment of Mass Casualities. Med. Sci. Pub. #4; Recent Advances in Med. & Surg.; Army Serv. Med. Grad. Sch., 190-202 1950-1953

IV Bacterial Factor in Protracted or Irreversible Shock

A certain small group of patients fail to respond to blood volume replacement therapy in traumatic shock. This is seen most frequently in protracted hemorrhagic shock or traumatic shock from some other cause than blood volume deficit. As noted earlier[15,16,17] war casuality shock shows a minimal incidence of this type of reaction. Some of the causes have been outlined. Another possible cause of low incidence of irreversible shock in war casualities may be the promptness with which transfusion was instigated (universal donor blood without cross-matching). Numerous investigators report that irreversible traumatic shock is seen more frequently in civilian practice. One group of investigators headed by Jacob Fine feel that the failure of reversibility of this type of shock may be due to a bacterial factor.[20,21] These investigators have been working for over ten years on this problem. Most evidence in support is experimental-produced by dog experiments. Fine et Al have devised a unique technique for hemorrhagic shock with nearly all variables controlled. With minimal sedation (½ mg/kilo), a cannula is placed in a femoral artery

and vein. The animal is bled into a reservoir containing heparin, and elevated above the heart so that bleeding stops when the arterial pressure reaches 30 mm Hg. Repeated (over 100 dogs) experiments show that if reservoir blood is rapidly transfused before 40% volume of self transfusion has occured-recovery is the rule. If after 40% of self transfusion, pressor response is not sustained and animal dies. If this group of animals were previously treated with antibiotics, (broad spectrum) 88% recovered while only 12% recovered in the control group.[22] Additional experiments with "inactivated" antibiotics showed no difference in effect of inactivated portion and controls. Thus proving that it was not other pharmicological properties of the antibiotics which were effective; but its bacteriostatic effect. Mainly upon this evidence, Fine believes that there is a bacterial factor in shock. There are several theories as to origin of this factor in cases such as hemorrhagic shock. Schwenberg[23] showed that radioactive E. coli could pass through the intestional barrier in dogs in uremia during peritoneal irrigation and produce shock and peritonitis. One fallacy in dog bacterial experimentation is that

clostridum are inherent in dog tissue especially liver. Mahoney[24] found that application of a Blalock crusher clamp to a dog's extremity caused no shock until the clamp was removed. This indicates that either a toxin was liberated or fluid infiltration into the affected extremity was the cause of the shock. Nelson and Noyes[25] showed however that blood cultures of dogs in hemorrhagic shock and control animals were similar in both showing approximately 22% incidence of positive cultures. It is necessary to keep in mind the fact previously descri ed, that toxins may be the source of shock rather than the bacteria themselves. One study[26] concluded that sub-clinical amounts of highly toxigenic bacteria may prod ce sufficient toxin to be a factor in development of circulatory failure either by promoting vascular fluid loss at site or trauma or acting directly on the cardiovascular system.

Part of the evidence which Fine uses in support of the bacterial factor in irreversible shock is exclusion of other possibilities. The vital organs have been blamed for failure. However the kidneys have been found to cause death from renal shut-down only after a period of 6-8 days. Cardiac output is

impaired due to reduced input and transfusions result in higher output till later stages or irreversibility. Chemical studies of adrenal function fail in incriminating this gland in shock. The sympathetic nervous system has been blamed and nor-epinephrine has been used to combat shock. This has resulted in conflicting results however and experiments show that is is not effective in influencing the course of irreversible shock.[27] The possible exception to this might be shock produced by coronary thrombosis. It has been found that nor-epinephrine increases the coronary flow in this condition. The primary disturbance here is <u>not</u> peripheral.

The liver has been blamed for failure in irreversible shock and some evidence supports this theory. Plasma prothrombin and fibrinogen levels in hemorrhagic shock have been found to be decreased. There appeared to be a decrease in regeneration of these substance during shock.[28,29] Cross circulation of the liver of a dog in hemorrhagic shock with a dog (healthy donor) is quite effective in changing the course of irreversible shock.[30] Certainly many of our defense mechanisms are originated in liver and its failure

in shock may explain why soldiers in good health are able to withstand more than debilitated, low protein, older patients in civilian practice.

Shorr et Al hypothesized the vasodepressor material theory in irreversible shock. However ferritin (isolated as vasodepressor material) failed to affect arterial pressure and survival period of hepatectomized and nephrectomized dogs in an experiment by Frank.[31] Absence of kidney or liver allowed no method of excretion or detoxification of this substance. Fine feels that there is a bacterial factor that the liver is not able to cope with in irreversible shock.

One discouraging finding in this work is that Hardy[32] of Texas was unable to repeat Fines' results of effect of antibiotics in preventing irreversibility of shock. He found no difference between control and experimental animals and 13% of both groups ultimately survived. Being from Texas however we might expect his findings to be different from any one elses.

Summary

This paper is an attempt to review and explain the various aspects where bacteria are concerned with secondary shock. Although some prefer to discard the term "shock" it persists as a frequently used discriptive clinical entity. Secondary shock or traumatic shock as defined here as a discrepancy between the vascular bed and the circulating blood volume. It produces hypotension, tachycardia, (rapid, thready pulse) and cool moist skin, pale cyanotic mucous membranes.

Bacteria in shock are divided here into primary sepsis, secondary bacterial invasion, and bacterial factor in irreversible shock.

Examples of shock following sepsis are cited. This appeared to be uncorrected by blood and fluid volume therapy and responded only to antibacterial and general supportive measures.

Secondary invasion of bacteria in traumatic wounds, burns, etc., may occur producing shock. Antitoxins and antibiotics are useful preventive measures when this may be anticipated. Broad spectrum antibiotics are most useful in these cases.

War medicine indicated that transfusion was practically the solution to shock at least as seen in battle wounds. Civilian practice has failed to correlate with this due probably to difference in

conditions of patients encountered and possibly to more and speedier transfusions given in war medicine.

Some investigators notably Jacob Fine feel that irreversibility in shock is the result of a bacterial factor. His evidence is mainly experimental and exclusion of other possibilities. One investigator failed to reach the same conclusion. Future evidence for or against this theory remains to be seen.

Thus it is seen that bacteria have a definite role in shock and where concerned the condition should be treated with that in mind. Shock responds poorly to fluid therapy when sepsis is the etiology. Such things as nor-epinephrine, arterial transfusions, etc., are merely "guilding the lily" and not attacking the basic cause in secondary shock.

War medicine shows effect of rapid and extensive transfusion of whole blood (universal donor) but in civilian practice other measures may be necessary.

Experimental evidence indicates bacteria may be influential in "irreversible shock" but evidence is as yet inconclusive.

(Appendix III)

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