I. THE C.S.T. PROGRAM

A. INTRODUCTION - THE PROBLEM

Shock appears to be the summation of the breakdown of many compensatory and feedback mechanisms of the organism usually resulting from severe injury, and is characterized principally by inability of the injured individual to maintain an adequate circulation. Because of this critical situation, most studies of shock have been directed primarily to circulatory factors, their cause and correction.

In injury where shock is a predominant factor, the use of the body's biochemical reserves, particularly those associated with homeostasis, determines to a large extent whether or not the patient survives. This requires careful metabolic

studies which had not been previously considered possible because of the urgency of obvious life-saving measures that must be immediately employed by the attending physician.

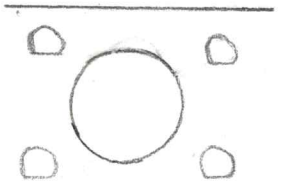
B. REASON FOR CREATING THE C.S.T.

1. SHOCK STUDIES IN ANIMALS

Over the years most shock studies have been carried out in animals for many obvious reasons and yet there has never been developed a reliable animal shock model to test therapy which is applicable to the true clinical situation. This lack of an experimental model has resulted in so many disjointed studies of shock and is one reason why the study of shock in animals has been so disappointing to us. Over the past 12 years, we have tried to devise a simple

hemorrhagic shock model and 900 dogs later, we are now only beginning to obtain a reproducable hemorrhagic shock model in the LD/50 range. Species differences also play a role in devising animal shock models. As a result in 1960, we decided that perhaps the best way to study shock was to look at people in shock - or, in other words, to paraphrase Pope, "The proper study of man is man". As our ideas gained momentum and the thought of creating a unit to study shock in man progressed, it seemed that piecemeal approaches by fragmentary studies were not likely to bring answers that were generally applicable to shock. Therefore, we felt a multi-disciplinary "system approach" as used by our engineering colleagues might be a better method of study especially, realizing that the observations

made could in no way interfere with resuscitation of the patient. To date, we have demonstrated that pertinent observations can be made on patients in severe shock without interferring with the resuscitation and that these same research methodologies have actually improved the resuscitation. Through our multidisciplinary "systems approach" we are now beginning to find causal relationships between inadequate tissue perfusion, hypoxia and organ failure.



In summary, most studies of shock in man have been directed primarily to circulation factors, their cause and correction and have not been aimed at the total problem involved; namely, the reaction of the body to trauma and the maintenance of life and repair of injury. In addition to local damage,

the systemic injury resulting from the breakdown of normal protective barriers lead to liver, pulmonary and renal complications. General infection, hemorrhage and other lesions of stress supervenes and the local lesion now becomes a general phenomena called shock.

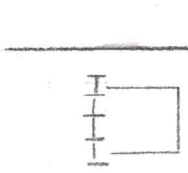
3 This search to understand the cause and effect

a.
b.

of shock has constituted the basis for a study now in progress at the University of Maryland Center for the Study of Trauma; namely, inadequate perfusion induced by trauma produces two major effects at the organ and tissue level.

a) subnormal supplies of oxygen and cellular nutrients cause profound changes in metabolism, incompatible with normal function.

b) failure to remove certain metabolic products produced by these changes in metabolism from the tissue at an adequate rate induce further deterioration.



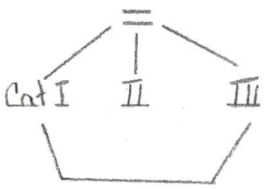
The changes in metabolism and deterioration of tissues are usually manifested by increased acidosis, by the change of various enzyme levels in blood and tissues and by other hypoxic changes in the body chemistry. In addition, there is a disruption of the body defense mechanisms often with the establishment of overwhelming sepsis. All of these processes, in turn, affect auto-regulatory mechanisms resulting in further deterioration and death.

To date we have looked at several physiological and biochemical parameters of patients in shock in an effort to identify which parameters are significant

and how these parameters can be used to better describe the phenomena of shock. Of a population of 600 shock patients admitted to the C.S.T. and studied during and after resuscitation, the first 300 are presented in this report.

Criteria 5A

5B



Our patient sourse was the emergency room, operating room, recovery room and intensive care units, as well as other hospitals. Patients of all the major classifications of shock were included.

All patients admitted to the C.S.T. were immediately placed in Category I, where the following studies were performed: vital signs, clinical laboratory studies, coagulation, and physiological and biochemical studies. In this category nearly all studies were performed initially before treatment, and at least every 6 hrs during the remainder of the time the patient stayed in Category I. These studies needed for patient care or evaluation of therapy were

performed more often if necessary. As the patient responded he was placed in Category II, where the same studies were repeated twice a day, and finally in Category III, where the studies were performed once every 24 hours until discharge. All studies were performed at the same designated time whenever possible in order to better define the interrelationsphis of the variables, but in no way interfered with resuscitation of the patient during the data collection.

THERAPY 6

The approach to therapy concerned itself with four major areas: 1. the primary process, 2. volume deficits, 3. acid base and electrolyte abnormalities and 4. specific organ failure. All patients therefore were treated according to accepted present day knowledge and standards..

METHODS 7
PERFUSION

During the study, pertinent physiological parameters

such as direct arterial and central venous pressure readings, cardiac output, total peripheral resistance, pulmonary function, ECG, blood gas, and urinary output studies were performed in order than the investigators might better evaluate the intensity of the shock and time relationships to the biochemical studies.

Some of the variables that will be presented relate to the liver as a possible target organ in shock, where we had once thought only the lung as being such an organ. Fifty-three autopsies on patients who had died in the C.S.T. have consistently pointed to the liver as an organ of failure in the shock syndrome. The 300 patients were groupsed according to final outcome, either lived or died, irrespective of the type of shock.

The statistical analysis was performed as follows: all observations of the variables presented include all readings from the time of admission until the time of discharge. The means of the variables for the two groups were computed, as well as other useful statistical parameters. The ranges displayed on the following slides represent the standard error of the mean and tell the investigator that, with a probability of 63%, the mean for all shock patients including those in our shock study, falls within this range. The scale picked was arbitrary for the convenience of making the graphs readable and accurate.

First, the physiological variables in order to have a better perspective of the biochemical observations.

9

The systolic blood pressure, the cardiac output, the total peripheral resistance and the central venous pressure of those that lived, above line, and died, below line, are as one might expect. All reflect venous stasis and poor perfusion. At autopsy this was manifest by evidency of central vein hypoxia of the liver and in extreme cases necrosis.

The total peripheral resistance demonstrates that the body is making every effort to maintain an adequate blood pressure at the expense of perfusion. There is a possibility that in the liver, the peripheral resistance may be high causing stasis or shunting to produce hypoxia because in carbon tetrachloride poisoning there is also a central lobular necrosis which can be prevented

by sympatholitic drugs. Protection can also be afforded the central lobule by using OHP in our experience.

10

The high blood pO_2 at death brings up the question of shunting and also inability of sick cells to utilize O_2 - most patients were on a respirator, particularly those who died. Extraction of O_2 - all again due to stasis.

11

SLIDE - pH falls as does the HCO_3. Why should the HCO_3 fall so low with vigorous therapy? Urea synthesis is one of the last liver functions to fail. Accelerated breakdown of protein, a characteristic of shock, and the BUN can reach levels of 60 mg% without renal failure - pre-renal azotemia. In our patients, urea clearance falls in all patients. The

damaged liver is perhaps over whelmed with protein breakdown products. Our studies show a definite release of amino acids in shock.

12 SLIDE - Inadequate tissue perfusion leads to increased lactic acid reflecting anaerobic glycolysis and is a factor in lowering the pH. This in turn depresses the myocardium and decreases the peripheral vascular response to catacholamines. Lactic acid is produced in muscle and carried to liver to be converted into pyruvic acid where it is utilized by the liver converting it to glycogen or oxidized to CO_2 and H_2O. A consistent lactic acid above 4 meq., in our hands, was usually associated with a high mortality.

13 SLIDE - ENZYMES

GOT - glutamic oxaloacetic transaminase

GPT - glutanic pyruvic t.

LDH - lactic dehyd.

MDH - malic dehyd.

All show effect of partial breakdown of cells, probably liver cells, with increase in permeability and enzyme release in the blood.

Other enzyme systems examined included the liver specific sorbitol dehydrogenase (SDH), isocitric dehydrogenase (ICDH - liver, heart), creatine phosphopkinase (CPK - striated muscle, brain), serum glutamic - oxalacetic transaminase (SGOT) and serum lacticodehydrogenase (SLDH), both with unbiquitous tissue distribution.

In patients who sustained injury within 24 hours of analysis, SDH and ICDH usually reach peak activity within the first 24 hours after injury while GOT and LDH peaked mainly on the second day.

In 4 patients studied with acute pure head injury, in the absence of hypotensive shock or any clinical signs or other conventional laboratory proofs of liver damage the SDH activity was increased by 200 to 500% by the time of admission. ICDH behaved similarly. These increases may be attributed to the stress reaction accompanying the injury.

We also routinely examine the serum of patients by acrylamide gel electrophoresis for isoenzymes. These gels are stained for protein and for the isoenzymes of lactic and malic dehydrogenase. The

isoenzyme pattern of LDH reflects the tissue origin of the serum enzyme. Although, in general, the LDH isoenzyme distributions do indicate the specific organs which have sustained injury or functional derrangement, in severe trauma or shock, serum LDH originates from tissues other than that sustaining the overt insult. For example, in severe head trauma, we have found hepatic LDH and in direct traumatic lesions of the liver we have observed the cardiac LDH isoenzymes.

14

In this SLIDE we see lactic dehydrogenase isoenzymes following rupture of the aorta in a patient who survived. Note the lactic dehydrogenase isoenzymes, bands 4 and 5, are present 24 hours after surgery but gradually disappear from the serum. However the lower 1,2, and 3 bands representing

the cardiac patterns remain.

15

UUUU

In the next SLIDE , staining the serum for protein has revealed the variable presence of a component migrating immediately behind albumin. Qualitatively, at least by visual inspection, the concentration correlates with the severity of trauma and the clinical status of the patient. As a glycoprotein and in electrophoretic mobility it resembles the "trauma" or "acute phase" protein found associated with experimental tissue injury in animals. Here we see an appearance and disappearance of the trauma protein after the patient gets well.

CLOT 16

SLIDE - The liver is responsible for all clotting factors, for the production of clotting as well as the fibrinolytic inhibitors except those from the gut. The changes we have

observed in shock have demonstrated a decrease in clotting factors, and an increase in fibrinolytic activity. Since clotting time relates to prothrombin time and prothrombin production by the liver and loss of fibrinogen also demonstrates a deficiency of liver production, one must then decide whether or not the clotting factors can be explained on increased consumption or decreased production. Increased consumption has been explained as intravascular clotting. However, we have been unable to verify this at autopsy. In addition coagulation and fibrinolytic changes in liver disease, such as cirrhosis, are about the same as those seen in the shock state.

17

SLIDE - Creatinine is associated with muscle hypoxia and poor renal function. Ammonia is converted to urea by the addition of CO_2 and

usually comes from putrefaction in the gut. Usually it is normally removed by a single passage through the liver and the normal arterial ammonia is less than 1 gamma. Since urea synthesis is impaired in shock, is the impairment secondary to stasis, shunting or hypoxia, bearing in mind that urea synthesis needs oxidative energy for conversion?

LIVER SLIDES

Histology of the liver in shock - there is marked congestion of the central vein area extending out of the periportal zone areas in some instances. This is recognized by dilated sinusoid filled with red blood cells. The liver cells are shrunken and the diameter is less than that of the sinusoids. In the severe cases there is central vein necrosis with a polynuclear cellular

response. There is no correlation with changes in liver, etc. There is no intravascular fibrin in the liver, lungs, and kidneys. We did not see multiple foci of cardiac necrosis nor hemorrhagic interopathy in the gut as described in those shock patients with cardiac disease.

The most consistent and noteworthy changes seemed to be in the liver. There were 44 of the 53 cases which could be reasonably evaluated; that is, the liver was adequately preserved and free of underly disease, such as cirrhosis or hepatitis.

18
25x

The most outstanding histological change was dilatation and congestion of the sinusoids

19
50x

and the hepatic veins. The sinusoidal dilatation was chiefly radial about the central zones and it was accompanied by narrowing of the liver cords.

In most severe cases the distension extended to involve the midzone, and there was interconnection or bridging of one central zone to the next in the plane of the section, 6-8 microns thick. At times the sinusoidal dilatation extended almost to the portal zones, but in most cases the periportal areas appeared normal.

20
MID ZONAL

In the most severe cases the central zone and at times the midzonal cells showed piknosis or loss of nuclei with dense eosinoplulio of their cytoplasm. Presumably at a slightly later stage the central zone parenchyoral cells were lost and replaced by numerous red blood cells. In the areas of central and/or midzonal necrosis the Kupfer cell nuclei were generally less affected.

21
RETICULA

A conspicuous increase in reticulum was found in the affected zones and paralleled the congestive

and necrotic changes. In the most extreme cases there was some thickening of the fibers and they stained more like collagen. Fatty change was seen in some of the livers and not in others, and did not seem to correlate with the shock or the other changes just described.

BIOPSY

SLIDE 1 - shows central lobular necrosis with congestion

SLIDE 2 - at a higher power - shows preservation of the Kupfer cells - no parenchymal cells around the central vein

SLIDE 3 - periphery of the same hepatic lobular shows necrosis of the hepatic parenchymal cells - nuclei is dark and the cytoplasm is deeply eosinophilic acute little evidence of hepatic parenchymal cell regeneration

GROSS SLIDE - shows a greatly enlarged liver with swollen edges and is deeply fial stain reflecting

intrahepatic cholestasis

GROSS

GROSS SLIDE 4 - shows area of yellow color which corresponds to the necrosis seen microscopically

AUTOPSY

SLIDE 5 - immediate autopsy - shows same as seen in first slide - necrosis of cells around the central lobular region - around the central vein

SLIDE 6 - high power - shows reminents of hepatic cell cytoplasm - dead cells

SLIDE 7 - periphery of lobular now shows hepatic cells with large nuclei prominent nuclei and one cell which has a double nuclei - shows regeneration changes.

CONCLUSION

Our studies have demonstrated that the correction of the blood volume, oxygenation of the blood, and fluid and electrolyte balance including acid base balance are critical but not life saving in many cases of shock. We have watched patients die in normal physiological, hematological, fluid and electrolyte balance. These data indicate that the metabolic abnormalities arising from impaired cellular function and pathological changes, especially in the liver, are significantly important in the ultimate course of whether a patient in shock will survive or die. A critical assessment of these metabolic functions may offer insight into the physiological derangements related to shock.

Based on our past experience, we now have a more specific outline of the principal problem of why some people die regardless of the therapy. For example, one might ask:

1. If you can correct volume deficits, blood gases alterations, electrolytes and acid base deficits and other hemodynamic variables, why should the patient die?

This question is now partially answered based on this information today and raises other questions. For example,

2. If you can re-establish the physiological balance, why can't the body restore metabolic balance?

3. Is general deterioration the result of irrepairable organ failure at the molecular

or cellular level?

Questions such as these point to further basic research into the areas of biochemistry, microcirculation, vasomotor mechanisms, and coagulation. A better understanding of these areas might then lead to a new concept of cellular replacement therapy based on giving enzymes, substrates, or other key ingredients necessary for survival until organ or tissue regeneration is complete.