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ABSTRACT REFERENCE LIST: REVIEWS OF PERTINENT LITERATURE IN SHO--ETC(U)
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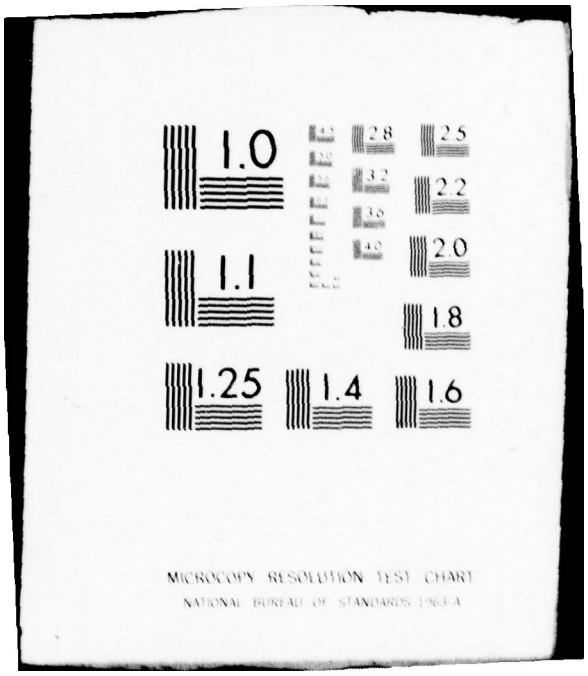
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Project NR 207-040

TECHNICAL REPORT NO. 138

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REVIEWS OF PERTINENT LITERATURE IN SHOCK

L. B. Hinshaw and J. S. Glasgow

University of Oklahoma Health Sciences Center
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1 June 1979

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(11) 1 June 1979 (12) 63 p.

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1. Hemodynamic effects of dopamine in septic shock with and without acute renal failure. K. Samii, J.-R. Le Gall, B. Regnier, G. Gory, and M. Rapin. Arch. Surg. 113: 1414-1416, 1978.

   Hemodynamic response to dopamine hydrochloride in septic shock with myocardial dysfunction was studied in 10 patients with normal renal function (group 1) and in 10 patients with acute renal failure (group 2). The control hemodynamic data were similar in the two groups. Dopamine in groups 1 and 2 induced significant ($p<.01$) and similar increases in cardiac index and mean aortic pressure. Group 1 had a smaller increase in heart rate (+16 %), than group 2 (+24%), but this difference was not significant. Stroke volume index had a significant increase in group 1 (+18%), whereas it did not increase significantly in group 2 (+4%); this difference of changes in stroke volume index between the two groups was significant ($p<.01$). This phenomenon suggests an increased chronotropic effect and/or a reduced inotropic effect of dopamine in patients with septic shock and acute renal failure.

2. Association of leukopenia and intestinal permeability with radiation-induced sensitivity to endotoxin. R. I. Walker and M. Porvaznik. Life Sciences 23: 2315-2322, 1978.

   Sensitivity to the lethal effects of endotoxin is increased after exposure to ionizing radiation in the hematopoietic death range. We hypothesized that leukopenia and altered intestinal permeability may be causative factors for increased sensitivity to endotoxin after irradiation. The presence of leukocytes and platelets was correlated with sensitivity of male B6CBF1 mice to 0.25 mg of Salmonella typhosa endotoxin administered ip. This study was conducted over the 10-day period following irradiation (1000 rads Co-60) and the beginning of deaths due to radiation alone. These data were then associated with the status of tight junction barriers (zonula occludens) between epithelial cells of the ileum. A biphasic pattern of sensitivity to endotoxin was observed in irradiated mice. Mice were resistant to endotoxin through day 2 after radiation, but sensitivity increased greatly (80% mortality) by day 3. Resistance increased by day 6 (6.7% mortality) and then dropped again by days 9 and 10 (100% mortality). Leukocyte numbers decreased 91% by day 2 (from 10,880 to 1,020 per mm^3) and further by day 3 (300 per mm^3). Leukopenia persisted through the duration of the experiment. Platelets began to decrease in number by day 5, and levels continued to drop until day 9. Disruption of some intestinal tight junctions was observed on days 1-5 after radiation. Junctional repair was evident by day 5. Repair was noted as extensive junctional elements on ablumenal membrane fracture faces. A combination of leukopenia and leakage of endotoxin from the intestine may account for increased sensitivity to endotoxin seen at day 3. Repair of the intestinal permeability barrier on day 5 coincided with reduced sensitivity to endotoxin. Later (7-10 days) bacteremia was present in host tissues, and mortality due to challenge with endotoxin was again increased. Disruption of some tight junctional barriers was seen again on days 9 and 10 after radiation.

3. Metabolic changes in burned patients. D. W. Wilmore and L. H. Aulick. Surg. Clin. N. Am. 58: 1173-1187, 1978.

The systemic metabolic and circulatory alterations following thermal injury are directed to support the healing wound. The open wound is an immediate priority of the body; structural and functional components of uninjured tissue undergo breakdown to provide energy, substrate, and micronutrients for the healing wound. Glucose is synthesized by the liver and utilized by granulation tissue. Wound blood flow is elevated and the injured surface is heated to enhance repair. These changes in systemic metabolism and directed by alterations in neurohumoral control; the exact mechanisms utilized by the wound to inititate these changes are presently not known.

4. Problems and complications of burn shock resuscitation. C. R. Baxter. Surg. Clin. N. Am. 58: 1313-1322, 1978.

The problems and complications of the fluid resuscitation phase of the treatment of major thermal burns are many and varied. Emphasis has been placed on the most important organ system responses commonly observed in the first week after injury. The efficacy of treatment and the lack of available treatment are outlined. The mechanical complications occurring from poorly selected and monitored fluid administration sites, complications of monitoring, problems of constrictive edema (usually in the extremities), airway problems, respiratory care, and innumerable other technical aspects were purposely omitted. While these problems and complications are extremely important and occur commonly in our experience, they are in the realm of technical performance of good emergency and intensive care medicine and their optimal management does not affect the problems and complications of the residual organ systems.

5. The limulus amebocyte lysate test: present and future application. F. D. Pearson. R. I. Med. J. 61: 315-319, 1978.

The limulus amebocyte lysate test is the most sensitive assay for bacterial endotoxins and routinely detects picogram amounts in solution. Bacterial endotoxins are lipopolysaccharides associated with the outer membrane of gram-negative bacteria. These endotoxins are also known as pyrogens. Since gram-negative bacteria shed significant amounts of these substances into their environment, a positive limulus test serves as an index to gram-negative bacterial contamination. Samples not revealing positive bacteriological culture are frequently found to contain endotoxins when assayed with the limulus test. There is general agreement amoung researchers that the LAL test should not be used for the detection of gram-negative septicemia or endotoxemia until the problem of inhibitor removal is much better understood and a standard test can be followed. The LAL test has also found experimental application in prediction of gram-negative septic episodes in burn patients.

6. Procoagulant activity of peritoneal leukocytes: effects of cortisone and endotoxin. A. J. Robinson, S. I. Rapaport, and S. F. Brown. Am. J. Physiol. 235: H333-H337, 1978.

Procoagulant activity of peritoneal leukocytes from rabbits given cortisone acetate, endotoxin, and both materials was measured in studies designed to test the hypothesis that cortisone acetate prepares rabbits for the generalized Schwartzman reaction by enhancing leukocyte procoagulant activity. Two types of peritoneal leukocyte suspensions were examined: mixed granulocyte-macrophage suspensions and macrophage suspensions. In both types, procoagulant activity could be accounted for by the number of macrophages in the suspensions. Cortisone alone did not affect the procoagulant activity, whereas endotoxin increased the procoagulant activity. Suspensions from animals given both cortisone and endotoxin varied in activity depending upon cell composition. Granulocyte-macrophage suspensions had less apparent procoagulant activity than suspensions with endotoxin alone. In contrast, macrophage suspensions--particularly sonicated suspensions--had greater procoagulant activity than those with endotoxin alone. The ability of cortisone acetate to increase macrophage procoagulant activity after endotoxin could represent one mechanism whereby cortisone acetate prepares rabbits for the generalized Schwartzman reaction after endotoxin.

7. Endotoxin and myocardial failure: role of the myofibril and venous return. F. D. Bruni, P. Komwatana, M. E. Soulsby, and M. L. Hess. Am. J. Physiol. 235: H150-H156, 1978.

The effects of gram-negative endotoxin-induced myocardial failure in the pentobarbital-anesthetized dog were examined by monitoring its influence on cardiac myofibrillar ATPase activity. Myofibrils were isolated from endo- and epicardial portions of the left ventricular wall. ATPase activities were determined in animals treated with 5 mg/kg endotoxin and monitored 5 hr, in animals monitored for 5 hr without endotoxin (controls), and in animals implanted with a unilateral femoral shunt and given endotoxin. No differences were seen in the activities between the endo- and epicardial portions of any preparation. Activity was significantly depressed in endotoxemic animals. Increasing venous return by 313±71 ml/min significantly increased coronary flow by reducing coronary vascular resistance and prevented any observed depression of myofibrillar ATPase activity. In in vitro studies, adding endotoxin directly to a myofibril preparation did not modify normal activity. It appears that the mechanical and myofibrillar dysfunctions are due to the action of endotoxin at sites not associated with the actomyosin ATPase, but may be due to the production of an intermediary agent in concert with a decreased venous return.

8. The effect of exogenous substrate on hepatic metabolism and membrane transport during endotoxemia. W. C. McDougal, S. Heimburger, D. W. Wilmore, and B. A. Pruitt, Jr. Surgery 84: 55-61, 1978.

Endotoxemia in dogs reduced hepatic uptake and biliary excretion of indocyanine green dye. This diminished active membrane transport with associated with reduced hepatocyte membrane potential difference. Studies of arteriovenous concentration differences and flow across the liver demonstrated that endotoxemia increased hepatic glucose and lactate production and decreased oxygen consumption. Correction

of this energy deficit occurred following infusion of glucose and insulin, but not after administration of isocaloric quantities of intravenous amino acids. The glucose-insulin infusion during endotoxemia shifted the liver back to an organ of glucose uptake, improved oxygen consumption, and provided the necessary energy for normal dye transport and maintenance of the normal membrane potential difference.

9. Prevention of endotoxin-induced changes in oxidative phosphorylation in hepatic mitochondria. R. G. DePalma, M. H. Glickman, P. Hartman, and A. V. Robinson. Surgery 82: 68-73, 1977.

E. coli endotoxemia affects hepatic energy linked function by uncoupling oxidation from phosphorylation. This study was done to determine whether a steroid, methylprednisolone sodium succinate (MPS), as well as excess substrate sodium succinate (SS), alters directly the effects of endotoxin on hepatic mitochondria. An assay system using α-ketoglutarate (α-Kg) was developed to test this hypothesis. Isolated rat hepatic mitochondria were first incubated in concentrations of MPS, ranging from 2.0 to 6.0 mg/ml. At these concentrations uncoupling identical to that occurring with addition of endotoxin resulted. However, a more dilute solution of MPS, 0.12 mg/ml, permitted normal mitochondrial function. Preincubation of MT in 0.12 mg/ml of MPS, as well as with sodium succinate, prevented endotoxin-induced uncoupling. Both endotoxin and steroid resulted in increased ATPase activity in the medium. While preincubation with MPS blocks the endotoxin effect, very high steroid concentrations alone are harmful. A direct action of steroids on mitochondria is evident, as well as a weaker protective effect due to excess substrate (α-Kg + SS). Since mitochondria are probably in direct communication with extracellular fluid, the assay system permits interaction of endotoxin, steroids, and substrates which mimic those which occur in vivo. The results of this study account for the previously reported variable effects obtained when steroids have been tested in vivo.

10. Effect of glucose-insulin-potassium on survival in experimental endotoxic shock. J. Manny, N. Rabinovici, N. Manny, M. Schiller, and H. B. Hechtman. Surg. Gynec. Obstet. 147: 405-409, 1978.

The effects of exogenous glucose, insulin and potassium on the survival rate in LD_{90}-induced endotoxemic shock was studied in dogs. In the control group, Group A, 1.75 mg/kg body wt of endotoxin was injected as a bolus into the femoral vein of 10 dogs. In the second group, group B, 15 dogs were treated with 3 gm of glucose, 1 unit of regular insulin and 0.5 mEq of potassium per kg body wt 30 min following the administration of same amount of endotoxin. Hemodynamic and metabolic measurements were conducted during a 5-hr period, and the survival rate was assessed after 48 hrs. The treatment with glucose-insulin-potassium in an LD_{90}-induced endotoxemia was followed by restoration of mean arterial blood pressure and a marked diuresis. While the dogs in group A had hypoglycemia and hypoinsulinemia develop, blood glucose and plasma insulin values in group B were maintained above normal levels. Arterial oxygen tension was improved, and pH values were returned to normal. In contrast to a 90% mortality in the control group, all dogs treated with glucose-insulin-potassium survived. These results indicate that glucose-insulin-potassium will reverse the hemodynamic, renal and metabolic derangements, maintain organ function and allow the survival of dogs subjected to a lethal dose of endotoxemia.

11. Endotoxin(s) and the liver. (Editorial). R. S. Munford. Gastroenterology 75: 532-535, 1978.

Are gram-negative bacterial endotoxins an important cause of liver injury? Do they contribute to the systemic manifestations of liver disease? These questions remain unanswered after many years of clinical interest and experimental investigation. Recent studies suggest a role for endotoxins in liver disease. Rats were protected from carbon tetrachloride hepatotoxicity by pretreatment with polymyxin B, a polypeptide antibiotic which inhibits endotoxin activity in several other experimental settings. Polymyxin B pretreatment also prevented death when the rats were subsequently given lead acetate, a compound which enhances the sensitivity of the rat to endotoxin toxicity. These results are consistent with previous data which suggest that endotoxins are released by gram-negative bacteria in the intestine, absorbed into the portal circulation, and detoxified by the normal liver. Impairment of hepatic clearance mechanisms, as may occur with acute liver injury caused by CCl_4 or other agents, allows gut-derived endotoxins to damage liver tissue and to reach the systemic circulation. This "spillover" endotoxin may then contribute to common extrahepatic manifestations of liver injury such as coagulopathy, hypotension, and renal insufficiency. Should this sequence lead us to conclude that endotoxins may be critical determinants of outcome in patients with liver disease? Unfortunately, the indirect methods used in this and other studies do not provide specific or quantitative assays for endotoxins. Investigators have sought such assays for decades, yet only in recent years has encouraging progress taken place. One important reason for this delay is the complexity of the substances which we call "endotoxins".

12. The mechanisms of thrombocytopenia in experimental gram-negative septicemia. M. I. Rowe, M. B. Marchildon, A. Arango, T. Malinin, and M. A. Gans. Surgery 84: 87-93, 1978.

The purpose of this study was to identify mechanisms responsible for the thrombocytopenia that accompanies gram-negative septicemia. Fifty-one piglets, 4 hr to 21 days old, were studied. Experimental animals were injected intra-arterially with live E. coli, and control animals with normal saline solution. Animals injected with bacteria had a progressive fall in platelet count to preinjection levels. No differences were found between experimental and control piglets in megakaryocytes number, nuclear generations, or morphology. There was a steady decrease in platelet aggregation to adenosine diphosphate (ADP), increasingly severe disruption of the number of circulating platelet aggregates in animals infused with E. coli. No platelet aggregates were observed to be occluding microcirculatory vessels. Small vessels in 1/3 of the pulmonary parenchyma frequently were obstructed by masses containing erythrocytes, leukocytes, platelets and fibrin. Single platelets were seen to be adherent to the lining of blood vessels. The architecture of platelets making up aggregates and of those adherent to blood vessels had relatively well-preserved ultrastructure. The platelet responses and light and electron microscopic findings after injection of E. coli were similar in splenectomized and nonsplenectomized animals and newborn and maturing piglets. It was concluded that the thrombocytopenia that developed in response to the injection of live E. coli was due primarily to platelet injury and destruction, and only platelets that were relatively intact functionally and morphologically took part in aggregation and adhesion.

13. Effect of nitroglycerin on peripheral blood flow distribution and venous return. R. I. Ogilvie. J. Pharm. Exptl. Ther. 207: 372-380, 1978.

Nitroglycerin infusions in anesthetized open-chest dogs with a long venous circuit and pump to maintain constant circulating flow induced dose-related reductions in mean arterial pressure (P_a), arterial resistance (R_a) and central blood volume or venous return to the heart without altering pressure-volume relationships of the venous circulation. Methoxamine infusions prevented the effect of nitroglycerin on P_a and R_a but did not abolish the acute reduction in venous return. Transient changes in blood volume after an acute reduction in right atrial pressure at a constant flow showed that blood was draining from two vascular compartments with different time constants, one fast and the other slow. Nitroglycerin induced dose-related changes in P_a without changing blood flow distribution to the compartments. A dose-effect relationship was observed for increases in total systemic vascular compliance. During infusion of nitroglycerin, 20 $\mu g/kg \cdot min^{-1}$, venous compliance of the slow time-constant areas was increased (34.0±11.0%) whereas compliance of the fast time-constant areas was reduced (-16.3±3.9%). Methoxamine abolished the effect of nitroglycerin on systemic vascular compliance but did not prevent the acute reduction in venous return. When circulating flow to slow time-constant areas was unchanged or increased, nitroglycerin infusions resulted in abrupt reductions in venous return. The results demonstrate the importance of peripheral blood flow distribution on the control of central blood volume, venous capacitance and venous return to the heart.

14. Improvement of pathological glucose tolerance by bradykinin in diabetics and in surgical patients. M. Wicklmayr, G. Dietze, B. Günther, L. Mayer, I. Böttger, R. Geiger, and K. Schultis. Klin. Wochenschr. 56: 1077-1083, 1978.

Intravenous glucose tolerance tests (GTT) were performed in 13 metabolically healthy patients at the first and second day after abdominal surgery. GTT were carried out during an additional infusion of bradykinin (BK) (80 µg/h) in 6 of these patients at the first day (group A) and in 7 patients at the second day (group B). Furthermore, GTT were performed in 6 patients with chemical diabetes with and without BK-infusion. In addition, the effect of BK on blood glucose concentration in the postabsorptive state was investigated in 9 maturity onset diabetics and in 5 healthy volunteers. As a control, another 9 diabetics received physiological saline. In both groups of surgical patients BK improved glucose tolerance (k-values: group A without BK 1.03±0.12, with BK 1.31±0.07; group B without BK 0.85±0.18, with BK 1.25±0.21). This was also true in chemical diabetics (without BK 0.81±0.03, with BK 1.08±0.04). While BK did not change blood glucose concentration in healthy volunteers, it reduced that of diabetics by 12.2±1.4% continuously during 100 min. No spontaneous drop of blood glucose was observed in diabetics receiving saline. These results are in good accord with the present view that kinins may play a role within the regulation of carbohydrate metabolism.

15. Temporal characteristics of insulin: glucose ratio after varying degrees of stress and trauma in man. M. M. Meguid, F. Aun, and J. S. Soeldner. J. Surg. Res. 25: 389-393, 1978.

We previously reported that the normal relationship between plasma glucose and serum insulin levels was altered for 48 hr after surgery. It is postulated that the inappropriately low insulin levels for the corresponding degree of glycemia after injury is influenced by the magnitude of trauma and for the time following trauma. Forty-one patients with major trauma and 11 with minor trauma were given varying quantities of glucose intravenously, while serial blood samples for insulin and glucose were analyzed for 5 days. To define the normal insulin to glucose relationship, 11 normal volunteers were infused with glucose solutions (5 to 30 g/hr). To evaluate the insulin to glucose relation, the slope of the regression line of insulin on glucose was calculated for 48 hr (early) and for the next 72 hr (late) for major and minor trauma (n=302) and for normals (n=115). The results show a highly significant insulin to glucose relationship as indicated by the slope of the regression line between major trauma and normal in both the early and late phases of trauma and between the early phase of minor trauma and the normal control group. No significant difference was found between the late phase of minor trauma and normal. After trauma, inappropriately low insulin levels for the degree of glycemia is a function of trauma severity and time. This plays a major role in the abnormal carbohydrate metabolism of injury.

16. Near-fatal and fatal anaphylactic reactions to insect sting. G. A. Peters, W. E. Karnes, and J. A. Bastron. Ann. Allergy 41: 268-273, 1978.

The relative importance of serious or fatal anaphylactic reactions to stinging insects and a failure of the older methods of desensitization to protect persons who have known hypersensitivty have been emphasized. Survival from severe reactions, with residual encephalopathy, has been reported infrequently. The pathogenesis of the encephalopathy associated with insect stings in general and with anaphylaxis in particular, has been thought by some to be a primary allergic response of brain tissue, and by others to be anoxia secondary to circulatory or respiratory (or both) failures. This report describes two patients with severe anaphylactoid reaction to stinging insects.

17. Naloxone reversal of endotoxin hypotension suggests role of endorphins in shock. J. W. Holaday and A. I. Faden. Nature 275: 450-451, 1978.

Endotoxins are known to result in the secretion of ACTH from the pituitary, presumably by activation of hypothalamic releasing factors. It has been shown recently that both ACTH and β-endorphin are stored in common pituitary sites and concomitantly regulated. It seems probable that endotoxins would therefore also release pituitary β-endorphin. Moreover, it seems likely that the established therapeutic efficacy of synthetic corticosteroids in the treatment of shock may be a partial consequence of their inhibitory effects on pituitary β-endorphin release. The enhanced sensitivity of adrenalectomised animals to shock states as well as to intravenous β-endorphin injections, both of which are attenuated by corticosteroid pretreatment, are also consistent with the hypothesis that endorphin release is important in the pathophysiology of shock. The effect of naloxone

in reversing the early hypotension of endotoxin shock suggests that naloxone may be efficacious in the treatment of septic shock. The possibility that the endogenous opiates may also be involved in the pathophysiology of other shock models is currently being investigated in our laboratory.

18. Bacteria and the liver. (Editorial.) J. P. Nolan. New Engl. J. Med. 299: 1069-1071, 1978.

An important and not widely appreciated function of the liver is that of a barrier to the passage of intestinal bacteria and their toxins into the systemic circulation. The portal blood is normally sterile, but in cirrhotic patients with defective clearance mechanisms, spontaneous Escherichia coli septicemia, presumably of gut origin, does occasionally occur. Of considerably greater consequence is the possibility that mild degrees of liver injury may alter the ability of the organ to detoxify the usually innocuous amounts of gut-derived bacterial endotoxins presented to it, and that this failure may lead to further hepatic damage and extraheptic effects as well.

Thus, in addition to its key role in maintaining homeostasis through its varied syntehtic, excretory and detoxification functions, the liver has the responsibility for cleansing both the arterial and the portal blood of bacteria and their toxic products. An inability to handle bacteria may lead to suppurative and rarely nonsuppurative disease, and a failure to detoxify toxic bacterial products may initiate or worsen liver injury.

19. Renal failure in liver disease: role of endotoxins and renin-angiotensin system. S. P. Wilkinson, I. K. Smith and R. Williams. The Kidney in Liver Disease. New York, Elsevier, 1978, pp. 113-120.

Evidence has been presented that renal failure in cirrhosis, fulminant hepatic failure, and obstructive jaundice is often due to systemic endotoxemia. In cirrhosis and fulminant hepatic failure the endotoxemia is probably due to failure of the liver to filter toxins absorbed from the gastrointestinal tract, but in obstructive jaundice is usually secondary to systemic gram-negative infection. Activation of the renin-angiotensin system by endotoxins might perpetuate the renal vasoconstriction that underlies the renal failure in cirrhosis.

20. Renal failure in cirrhosis: current views and speculations. S. P. Wilkinson and R. Williams. Adv. Nephrol. 7: 15-32, 1977.

Conclusions:

(1) Renal failure is a common complication of advanced cirrhosis and its occurrence in some instances is of direct clinical relevance.

(2) Often the renal failure is characterized by intact tubular structure and function ("functional renal failure"), the pathogenesis of which appears to be a renal vasoconstriction.

(3) There is little evidence to support the widely held view that the renal vasoconstriction is secondary to pooling of blood in the splanchnic circulation.

(4) Mounting evidence from several different sources suggests that it is due to an active vasoconstriction caused by circulating endotoxins, the endotoxemia being due to failure of the liver to filter the toxins absorbed from the gut into the portal circulation.

(5) The renal vasoconstriction may be perpetuated by activation of the renin-angiotensin system within the kidney.

21. Prostaglandins; their biological and pharmacological role. H. Vapaatalo and J. Parantainen. Med. Biol. 56: 163-183, 1978.

The biological and pharmacological roles of prostaglandin system are reviewed. The most recent and important finding is the isolation and characterization of endoperoxides, thrombosanes and prostacyclin. In many respect they seem to be even more effective than the original prostaglandins and could explain many actions previously attributed to prostaglandins. Prostaglandins, endoperoxides, thromboxanes, and prostacyclin seem to have important physiological and pathophysiological roles, e.g. in the cardiovascular, gastrointestinal and reproductive systems, the skin, and the central nervous system, as well as in inflammatory, immunological and metabolic reactions. Thus, prostaglandin-like substances, their analogues, prostaglandin antagonists, and the drugs that affect prostaglandin synthesis present good prospects for the treatment of many diseases affecting these systems. The mode of action of most anti-inflammatory and analgesic drugs can be explained by actions on the prostaglandin system. New potent and selective regulators of the prostaglandin system are being investigated and more indications are being found for using existing drugs. Although the field is generally promising, there are many contradictory findings. This calls for a cautious interpretation of the many interesting observations.

22. Association of sepsis with an immunosuppressive polypeptide in the serum of burn patients. M. B. Constantian. Ann. Surg. 188: 209-215, 1978.

One hundred ninety serum samples from 51 burned patients were tested for immunosuppressive activity which might explain decreased host immune competence following thermal injury. The serum from a variable but significant percentage of these patients suppressed the response of normal human peripheral blood lymphocytes to phytohemagglutinin. The occurrence of immunosuppressive activity paralleled the severity of the injury. Ten of ten severely burned patients (severity index <40), but only 20 of 30 patients with index 10-39.9, and three of 11 patients with Index 0-9.9 developed suppressive serum. Differences between these groups were significant ($p<.05$). In all 19 patients who became septic, immunosuppressive serum activity immediately preceded or coincided with the septic episode. In contrast to the effect on lymphocytes, burn sera stimulated fibroblast proliferation. Immunosuppressive activity did not correlate with serum cortisol levels, blood transfusion, protein-calorie malnutrition, or anesthesia. Suppressive sera were not cytotoxic. A majority of the active serum factor(s) was contained in a low molecular weight (<10,000 daltons) polypeptide subfraction.

23. The effect of fluid infusions upon serum protein concentrations during hemorrhagic shock. L. C. Getzen, E. W. Pollak, A. J. Clifford, and E. F. Wolfman, Jr. Surg. Gynec. Obstet. 146: 745-749, 1978.

Of 24 dogs subjected to hemorrhagic shock, 12 resuscitated with i.v. infusions containing 2.5% human serum albumin maintained significantly higher, $p<0.05$, serum albumin levels than did 12 others treated with Ringer's lactate solution, with or without 50% dog plasma. These differences persisted for as long as six weeks after hemorrhage. Dogs resuscitated with Ringer's lactate solution and 50% dog plasma had significantly higher serum globulin levels than did the dogs receiving 2.5% albumin containing infusion during the first 3 days after hemorrhage. The simultaneous addition of 5% glucose, potassium chloride and hydrocortisone sodium succinate to the infusion of dogs receiving 2.5% albumin in Ringer's lactate solution did not provide significant alterations in the serum concentration of protein and protein fractions when compared with those of dogs receiving only 2.5% albumin in Ringer's lactate solution.

These findings corroborate the suggestion of a capillary leak of serum albumin into the interstitial space during hemorrhagic shock that persists for at least one week after hemorrhage. The administration of albumin containing solutions during the initial stages of hemorrhagic shock counteracts this albumin loss.

24. **Inactivation of endotoxin by Limulus amoebocyte lysate. R. Nachum, S. E. Siegel, J. D. Sullivan,** Jr., and S. W. Watson. J. Invert. Pathol. 32: 51-58, 1978.

The inactivation of bacterial endotoxin by aqueous extracts (Limulus amoebocyte lysate) of the circulating blood cells (amoebocytes) of the horseshoe crab, Limulus polyphemus, is described. Active extracts were obtained by heating Limulus amoebocyte lysate (LAL) to 60°C for 20 min to denature the clotting enzyme, rendering the LAL incapable of gel formation in the presence of endotoxin. Endotoxin inactivation was assayed using the Limulus amoebocyte lysate test and by rabbit bioassay. Inactivation of endotoxin with heated extracts of LAL was suggestive of enzymatic mediation, as indicated by dependence on time, temperature, pH, and the kinetics of inactivation. Endotoxin inactivation occurred over a broad pH range, 4.5-8.5, with the optimum at a pH of 6.1. Temperature optima were between 47°C and 50 C, with observed activity between 0° and 65°C. Ionized calcium was inhibitory to endotoxin inactivation with heated extracts of LAL, with partial inhibition at 0.001 M calcium and complete inhibition at 0.02 M calcium. Other divalent cations (Mg, Ba, Mn, and Cu) were also found to inhibit the inactivation of endotoxin. Similarities between the endotoxin-inactivating system of L. polyphemus and those described to be present in mammalian and lower vertebrate sera are discussed.

25. Endotoxin receptor site. I. Binding of endotoxin to platelets. S. Washida. Acta Med. Okayama 32: 159-167, 1978.

Binding of bacterial endotoxin to platelets, erythrocytes, lymphocytes and granulocytes was examined by using diffusion dialysis. Platelets, erythrocytes, lymphocytes and granulocytes were fractionated from normal human blood and the binding of endotoxin (LPS: Lipopolysaccharide of E. coli) to each cell fraction was measured at 4°C and the binding efficiency was expressed as a binding index (%4°C±SD). The binding index for each cell fraction was as follows; 10.2±1.6 for platelets, 1.0±0.9 for erythrocytes, 4.3±1.6 for lympohcytes and 10.0±1.5 for granulocytes (n=11) respectively. Since a platelet possesses a small cell surface area compared with other cells, it was clear that the endotoxin bound preferentially to platelets in vitro. The binding mechanism to the platelet cell surface was suggested to be direct binding of endotoxin to the receptor on platelet cell membrane rather than through an immunologically activated mechanism.

26. Endotoxin receptor site. II. Specificity of endotoxin receptor of platelets and sensitivity to endotoxin in vivo. S. Washida. Acta Med. Okayama 32: 217-223, 1978.

The biological specificity of the endotoxin receptor on platelet membranes was examined. The binding indices of platelets in experimental endotoxemia which was induced by intravenous administration of endotoxin (Lipopolysaccharide of E. coli, Difco) to rabbits were found to be 30% of the control at 60 min after the injection. The result suggests that the endotoxin receptor of platelets was already occupied. The binding indices of human platelets were measured after pretreatment with pharmacologically active substances which were assumed to effect platelet activity. The binding of LPS to platelets showed competitive inhibition at pharmacologically effective doses, but other substances merely inhibited platelet activity. One interpretation is that there is a common receptor on platelet cell membranes for lipopolysaccharide of E. coli and endotoxin. The sensitivity to endotoxin in vivo and binding indices of platelets were examined in rabbits and guinea pigs since their response to endotoxin is almost opposite with regard to sensitivity. The binding indices of platelets from rabbits and guinea pigs showed a positive correlation with the endotoxin sensitivity. Those findings indicate that platelets play a key role in vivo in the clinical course of endotoxemia.

27. Glucose and lactate metabolism in experimental septic shock. R. R. Wolfe and J. F. Burke. Am. J. Physiol. 235: R219-R227, 1978.

We have investigated the effect of an intra-arterial injection of approx. 10^{10} live E. coli on glucose and lactate metabolism in the guinea pig. Glucose and lactate kinetics and oxidation were measured in conscious, unrestrained animals by means of the primed constant infusion of either [6-^{3}H]- and [U-^{14}C]glucose (infused simultaneously) or [U-^{14}C]lactate. The ability of livers from septic animals to produce glucose from lactate was also examined in isolated perfused livers taken from animals at 3 and 15 hr post E. coli and compared to glucose production in livers taken from

control animals. In vivo, there was a sustained increase in glucose production over the first 6 hr post E. coli, and hyperglycemia was evident. In contrast, the in vitro capacity for glucose production was significantly impaired at 3 hr post E. coli. At 14 hr, glucose production was not depressed in vivo below the control value, but, nonetheless, hypoglycemia was evident. The in vitro gluconeogenic capacity was reduced at 15 hr. Thus, factors were operative in vivo that enabled glucose production to remain at the control level or above despite a direct inhibitory effect of E. coli on glucose production evident in the isolated liver. An increased rate of recycling of glucose carbons (as lactate) back to the liver for reincorporation into glucose, rather than being directed to CO_2, appeared to be one such factor.

28. Effects of slow intravenous administration of endotoxin on blood cells and coagulation in dogs. A. O. Aasen, J. Dale, K. Ohlsson, and M. Gallimore. Eur. Surg. Res. 10: 194-205, 1978.

Endotoxemia triggers an intravascular coagulation process both in man and other mammalian species. This phenomenon is thought to be mediated by at least three mechanisms: (1) activation of the intrinsic pathway of coagulation through Hageman factor, either directly or indirectly through the induction of endothelial damage; (2) release of clot-promoting components from cellular elements of blood; and (c) release of tissue substances which initiate thrombin formation through the extrinsic pathway of coagulation. Although the implication of these mechanisms has been extensively studied, their significance is still not fully understood.

Endotoxin shock was induced in dogs by slow administration of a lethal dose of E. coli endotoxin. During the 3-hr infusion period a state of disseminated intravascular coagulation (DIC) was noted. The drop in platelets and leukocytes was the most rapid and pronounced effect of the infusion, while consumption of coagulation factors occurred more slowly. Activation of the extrinsic and intrinsic pathways of coagulation appeared to be closely parallel. Concomitantly increasing amounts of fibrin(ogen) degradation products were detected, while soluble fibrin monomers were observed only inconstantly. Intravascular hemolysis was slight and occurred in the late stages of shock, and could not have influenced the development of DIC.

29. A new model for the study of septic shock. A. Perbellini, C. H. Shatney, D. J. MacCarter, and R. C. Lillehei. Surg. Gynec. Obstet. 147: 68-74, 1978.

Septic shock was produced in 28 healthy mongrel dogs by injecting 10^8 Escherichia coli organisms per kilogram into the gallbladder following division of the cystic artery and duct. Based upon the circulatory responses and the mortality, two distinct groups emerged. In one, the cardiac index decreased significantly, and the total peripheral resistance was elevated. In the other, the cardiac index increased significantly, and the total peripheral resistance was significantly lower. The average survival time in the former group was 3 days, and in the latter, 5 days. The physiopathology of this model is remarkably similar to that of human septic shock. Studies are planned to further describe this model to increase its utility in the study of septic shock.

30. Peritonitis and intraabdominal abscess: An experimental model for the evaluation of human diseases. R. L. Nichols, J. W. Smith, and E. R. Balthazar. J. Surg. Res. 25: 129-134, 1978.

An economical, reproducible experimental model of intraabdominal sepsis in rats has been developed. This model was produced by placing varying amounts of human fecal material within gelatin capsules, which were then surgically placed within the peritoneal cavities of rats. The type of intraabdominal sepsis produced varied according to the amount of inoculum introduced. The full spectrum of sepsis produced was similar to that seen in human peritonitis and intraabdominal abscess formation. This model is suitable for and is presently being used to evaluate the efficacy of the various antibiotic schemes currently used in the treatment of human intraperitoneal infections.

31. Unchanged pulmonary capillary filtration coefficients after Escherichia coli endotoxin infusion. J. D. Gabel, R. E. Drake, J. F. Arens, and A. E. Taylor. J. Surg. Res. 25: 97-104, 1978.

The pulmonary capillary filtration coefficient ($K_{f,c}$) was measured in intact, anesthetized dogs before and after the intravenous administration of alloxan and E. coli endotoxin. The method used to measure $K_{f,c}$ was that of determining the capillary filtration rate by analyzing the weight transient following a change in capillary pressure (ΔP_c) and dividing the initial filtration rate by ΔP_c. In four dogs given 75 mg/kg of alloxan, the $K_{f,c}$ increased 10-fold. This indicated that the capillary membranes were damaged by the alloxan and that, by using this method of measuring $K_{f,c}$, changes in $K_{f,c}$ were easily detected. The $K_{f,c}$, measured after a 3-hr continuous infusion of a total of 4 mg/kg of E. coli endotoxin [0.35 ± 0.21 (SD) ml/min/mmHg/100 g], was not different from the value found in the same animals before the endotoxin (0.33 ± 0.29). Since the $K_{f,c}$ is a sensitive indicator of capillary membrane pore size, these results strongly suggest that E. coli infusion did not damage the pulmonary capillary membrane.

It has long been recognized that an increase in capillary pressure, independent of changes in membrane permeability, can cause pulmonary edema. Such an increase in capillary pressure could be caused by an increase in resistance. The results of these experiments clearly show a twofold increase in total pulmonary vascular resistance after E. coli endotoxin infusion. This increased pulmonary vascular resistance coupled with the lack of evidence of capillary permeability change reopens the question of the etiology of the respiratory failure associated with sepsis.

32. Insulin and the glucoregulatory alterations of RES depression. A. M. Hadbavny, B. J. Buchanan, and J. P. Filkins. J. Reticuloendo. Soc. 24: 57-62, 1978.

Depression of RES function in male Holtzman rats via either lead acetate or colloidal carbon blockade produced elevations of basal and, especially, glucose-stimulated serum insulin levels. Functional evidence for a hyperinsulinemic state after lead treatment included sensitization to lethal insulin-induced hypoglycemia, increased glucose tolerance, and enhanced whole body glucose oxidation. A role for the RES in modulation of circulating insulin levels is proposed.

33. Endotoxic shock in the rabbit: the effects of prostaglandin and arachidonic acid administration. J. T. Flynn. J. Pharm. Exptl. Ther. 206: 555-566, 1978.

A rabbit model was used to determine the effects of prostaglandins and arachidonic acid on cellular integrity and survival during endotoxic shock. Prostaglandins A_2, E_1 and $F_{2\alpha}$ were infused i.v. at a rate of 1.0 µg/kg/min for 105 min beginning 15 min after the administration of an LD_{60} dose of E. coli endotoxin. While each of the prostaglandins tested significantly attenuated the accumulation of lactic acid dehydrogenase in the plasma of shocked animals, none were able to protect against the increase in the plasma activities of glutamic pyruvic transaminase or cathepsin D during the shock state. Prostaglandins A_2, E_1 and $F_{2\alpha}$ did not significantly enhance the survival of the treated animals as compared to vehicle-treated controls. In contrast, arachidonic acid (15 µg/kg/min i.v.) significantly prevented the accumulation of lactic acid dehydrogenase and glutamic-pyruvic transaminase activities in the plasma of shocked animals, and also significantly increased the number of survivors in this group 48 hours after the endotoxin administration. In summary, while the treatment of endotoxic rabbits with prostaglandins of the A, E and F series was of no survival value, the treatment of these animals with a substrate of the prostaglandin synthetase complex resulted in a dramatic increase in the survival rate. The mechanism of action of arachidonic acid in this regard is not clear.

34. Temporary cardiopulmonary bypass for the treatment of endotoxic shock. U. Ito, A. Wakabayashi, J. E. Guilmette, and J. E. Connolly. Am. J. Surg. 136: 80-84, 1978.

New Zealand white rabbits were employed in the laboratory to evaluate the efficacy of temporary cardiopulmonary bypass in the prevention of pulmonary injury from endotoxin. Partial cardiopulmonary bypass using peripheral cannulation was carried out for 15 min after intraarterial administration of E. coli endotoxin of LD_{90} doses. A significantly better long-term (1 month) survival rate of the treated animals (60%) versus the untreated animals (10%) as well as less severe pulmonary changes in those that succumbed after treatment were observed. It would appear that temporary cardiopulmonary bypass by peripheral cannulation warrants further study in the treatment of patients identified early as suffering from otherwise irreversible septicemic shock.

35. Influence of methylprednisolone on ultrastructural and cytochemical changes during myocardial ischemia. R. S. Decker and K. Wildenthal. Am. J. Path. 92: 1-22, 1978.

Occlusion of the circumflex branch of the coronary artery of rabbit hearts for 45 min elicits structural and cytochemical changes in myocytes similar to those observed in ischemic dog myocardium, which are indicative of irreversible cell injury. When methylprednisolone is administered prior to occluding the artery, myocytes are transiently protected and many of the electron microscopic signs of irreversible damage are delayed for 15 min or more. During this period, the steroid preferentially protects mitochondria, lysosomes, and sarcolemma from the ischemic changes that normally develop. However, some other events, including depletion of glycogen and margination of nuclear chromatin, are only minimally influenced by the therapy, if at all. In all hearts, treated and untreated, the development of severe cell damage, whenever it occurs, is closely associated with cell swelling, mitochondrial dilation with concomitant appearance of amorphous osmiophilic densities, and abnormalities in and, ultimately, disappearance of lysosomes, suggesting that damage to cell membranes is a central event in the progression of reversible injury to irreversible infarction and that protection of membrane integrity should be a reasonable aim in efforts to ameliorate or delay ischemic injury.

36. Hemodynamic effects of intravenous phentolamine in low output cardiac failure. Dose-response relationships. M. A. Stern, H. K. Gohlke, H. S. Loeb, R. P. Croke, and R. M. Gunnar. Circulation 58: 157-163, 1978.

Afterload reduction using vasodilators is becoming a widely used and valuable adjunct in the management of patients with severe heart failure. Sodium nitroprusside has become one of the more popular intravenous vasodilators. Although the acute clinical and hemodynamic responses to nitroprusside are frequently dramatic, its extended use over several days may be associated with toxicity due to accumulation of thiocyanate. Additionally, some patients do not respond adequately to nitroprusside. For these reasons, the efficacy of alternative vasodilators should be assessed in patients with severe heart failure. Among such agents, the alpha blocker phentolamine has been shown to exert beneficial hemodynamic effects when given intravenously to patients with heart failure. Previous studies have usually assessed the effects of phentolamine infused at a single dose. This study evaluates the acute hemodynamic effects of intravenous phentolamine infused at increasing dose levels in 19 patients with stable, chronic low output cardiac failure.

Nineteen patients with chronic low output cardiac failure were studied before, during and after infusion of phentolamine in doses of 10, 20, 30 and 40 μg/kg/min. Significant reduction of left- and right-sided pressures and increases in cardiac index and heart rate (HR) were present within 15 min of starting phentolamine at the 10 μg/kg/min dose. Minimal additional effect was observed at 30 minutes. Increased dose from 10 to 20 μg/kg/min resulted in small but significant ($p<0.05$) additional reduction in pressures and increases in HR.

No additional significant changes occurred at doses of 30 or 40 µg/kg/min. Significant hemodynamic changes persisted for at least an hour (53±3 min) after the phentolamine infusion was discontinued. Near maximal hemodynamic effects occur within 15 min of starting phentolamine infusion and can be achieved at doses of 10 to 20 µg/kg/min. Increased HR during phentolamine infusion may limit its usefulness in patients with ischemic heart disease.

37. The adrenergic mechanism of the haemodynamic effects of massive doses of hydrocortisone in controlled haemorrhagic shock in the dog. E. Häggendal, M. Lindfors, and D. Lundberg. Acta Anaesth. Scand. 22: 208-214, 1978.

Haemorrhagic shock was induced in anaesthetized dogs by bleeding them into a blood reservoir system. By adjusting the blood level of the reservoir at a certain distance over the heart level the mean arterial blood pressure was kept at 6.7 kPa (50 mmHg). As has been found earlier, massive doses of hydrocortisone (80-560 $mg \cdot kg^{-1}$ body weight) caused a dose-dependent decrease in the total peripheral resistance. The degree of vasodilation distinctly increased during concomitant alpha-receptor blockade induced by phenoxybenzamine. The beta-receptor blocking drug propranolol efficiently inhibited the vasodilation caused by hydrocortisone and phenoxybenzamine. The findings fit with the hypothesis that massive doses of hydrocortisone induce an increased stimulation of the adrenergic $beta_2$-receptors of the vascular smooth muscles.

38. Depression of prostaglandin synthetase activity in kidney medulla by Shigella endotoxin injected intravenously. P. Bhattacherjee and A. Phylactos. Biochem. Pharmacol. 27: 807-808, 1978.

Prostaglandin synthetase activity in ocular tissues increases in experimental ocular inflammation produced by intravitral injection of Shigella endotoxin. Similar alteration of the enzyme activity in ocular tissues was also observed during immune-complex reactions. These findings are contrary to the well established facts that lipopolysaccharides inhibit various enzyme systems including those involved in carbohydrate metabolism and tryptophan oxygenase and tyrosine α-ketoglutarate transaminase. The inhibitory effect of endotoxin on enzyme activity is probably due to the cell damage caused by acidosis, reduced mitochondrial respiration and breakdown of homeostasis in response to bacterial lipopolysaccharides and recently, inhibition of hepatic microsomal drug metabolising enzymes in endotoxin injected rats has been reported. The purpose of the present study was to examine the effect of intravenously administered Shigella endotoxin on kidney microsomal prostaglandin synthetase activity.

It is obvious from the results that Shigella endotoxin administered intravenously suppressed the prostaglandin synthetase activity in the kidney medulla. The precise mechanism by which Shigella endotoxin exerts an inhibitory effect on this and other enzyme systems is yet to be elucidated.

39. Experimental meningococcal septicemia: effect of aspirin therapy. F. G. Dalldorf, J. C. Jennette, G. W. Upton, and J. C. Tullar. Arch. Pathol. Lab. Med. 102: 515-517, 1978.

In previous studies we have presented morphological evidence that the terminal shock-like phase of fatal meningococcemia is caused by the occlusion of the pulmonary microcirculation with thrombi composed of platelets, leukocytes, and fibrin. We have also shown that in experimental meningococcemia, pretreatment of rabbits with heparin sodium prevents fibrin formation but does not influence the cellular pulmonary thrombi and does not prolong survival. If our theory is correct, drugs that inhibit platelet aggregation and leukocyte adhesion in rabbits should prolong life. The present experiment demonstrates that pretreatment with a small dose of aspirin doubles the survival time without altering the mortality.

40. Vasodilator therapy in clinical sepsis with low output syndrome. F. B. Cerra, J. Hassett, and J. H. Siegel. J. Surg. Res. 25: 180-183, 1978.

Eight patients presented with gram-negative septicemia and septic shock. After appropriate medical and surgical therapy, they underwent a transition from a high cardiac output, low TPR state into a low cardiac, high TPR state with a significant fall in oxygen consumption. This state was refractory to maximized volume expansion and inotropic support. Vasodilator therapy with nitroglycerine paste was initiated along with intense, longitudinal physiologic assessment. All patients had a significant fall in TPR, rise in cardiac output, improvement in contractility, and increase in oxygen consumption. Five of the eight patients survived. Vasodilator therapy with nitroglycerine paste is an effective mode of treating the often catastrophic complication of myocardial decompensation in gram-negative septic shock.

41. Correction of hepatocellular dysfunction during endotoxemia. S. L. Heimburger, W. S. McDougal, D. W. Wilmore, and B. A. Pruitt, Jr. J. Surg. Res. 24: 442-448, 1978.

Although a variety of metabolic and circulatory events occur during gram-negative bacteremia, the liver has gained increasing attention as the primary target organ during sepsis. Gram-negative organisms, or their endotoxins, may decrease the aerobic capacity of the liver, impair hepatic gluconeogenesis and ketogenesis, and diminish membrane transport of substances into the hepatocyte or impair active excretion of substances in the bile. The usual laboratory tests of liver function often fail to reflect these metabolic abnormalities, and more precise measurements of hepatocyte function are needed to quantitate abnormal liver function and assess the effect of specific therapy in critically ill patients.

In summary, the observation of decreased hepatocyte active transport and increased membrane permeability which has been observed in man has

been confirmed in an animal model. These alterations in ICG kinetics cannot be attributed to changes in blood flow, dye distribution space, or other systemic factors. These alterations in hepatic energetics can be returned toward normal by the simultaneous administration of glucose and insulin. In this model system, endotoxin is thought to have a direct effect on the hepatocyte, which markedly alters cellular energetics and hepatocyte transport, and may account for the progressive changes in hepatic function which are frequently observed in critically ill infected patients.

42. The relationship of glycogen, glucose, and lactate to mitochondrial dysfunction in late hemorrhagic shock. R. S. Rhodes. J. Surg. Res. 24: 507-512, 1978.

The relationship of glycogen depletion, hypoglycemia, and lactic acidemia to mitochondrial dysfunction in late hemorrhagic shock was examined. Anesthetized rats were hemorrhaged through a femoral artery catheter using a modified Wiggers' technique. Animals were sacrificed after 0, 15, 30, 45, or 60% uptake of the maximum shed volume. Hepatic mitochondrial energy-linked functions, hepatic glycogen and lactate, and serum glucose and lactate were determined at the time of sacrifice. The frequency of uncoupled oxidative phosphorylation increased with percentage of shed blood taken up. Although blood glucose was significantly lower in animals in whom uncoupling occurred, there was a wide range of values and a poor coefficient of correlation. A borderline difference between the coupled and uncoupled groups was noted with glycogen, and no difference was observed with blood or hepatic lactate.

Glycogen depletion, hypoglycemia, and lactic acidemia although all manifest in late, experimental, hemorrhagic shock do not cause hepatic mitochondrial dysfunction. Effective treatment of late shock requires a more precise definition of the underlying metabolic pathology.

43. Intracellular sodium and potassium changes in vascular smooth muscle during hemorrhagic shock. B. Day and S. M. Friedman. Surg. Gynec. Obstet. 147: 25-26, 1978.

The vascular smooth muscle cell sodium and potassium changes occurring in hemorrhagic shock were studied in rats subjected to hemorrhagic shock at 30 mmHg for a 2-hr period. A new ion exchange method, based upon the substitution of lithium for extracellular sodium was used to measure the intracellular sodium and potassium. A significant rise in cell sodium and fall in cell potassium levels occurred. These changes suggest that vascular smooth muscle cell membrane function is impaired in hemorrhagic shock. The normal homeostatic vascular responses to hemorrhage may be significantly affected by these changes.

44. Nitroprusside prevents adverse hemodynamic effects of vasopressin. S. Gelman and E. A. Ernst. Arch. Surg. 113: 1465-1471, 1978.

The influence of vasopressin and sodium nitroprusside on liver circulation was investigated in 18 dogs. Cardiac output was determined by the thermal dilution technique using a Swan-Ganz catheter. Hepatic artery and portal vein flows were measured with electromagnetic flowmeters. The infusion of vasopressin (0.01 unit/kg/min) caused a 13% increase in mean arterial pressure, a 38% decrease in cardiac output, a 57% decrease in portal blood flow, and a 35% decrease in portal pressure. Hepatic artery blood flow initially decreased, then increased, and eventually exceeded the baseline value by 25%. The addition of sodium nitroprusside infusion (10 μg/kg/min) returned the mean arterial pressure to baseline value and increased cardiac output to 83% of baseline value. Portal blood flow remained unchanged, even though an additional decrease in portal pressure of 11% and a further increase in hepatic artery blood flow of 45% were observed.

Nitroprusside minimizes the undesirable effects of vasopressin and augments the desirable ones in normal dogs. The combination of these drugs may be more beneficial to patients with esophageal and gastrointestinal bleeding than vasopressin alone.

45. Inhibition of lethality in endotoxin-challenged mice treated with zinc chloride. S. L. Snyder and R. I. Walker. Infect. Immun. 13: 998-1000, 1976.

The success of previous investigators in reducing mortality to endotoxin-induced shock by using lysosomal stabilizing agents and antiproteases prompted us to test the hypothesis that zinc could protect against lethality induced by endotoxin. There is evidence that the zinc ion (Zn^{2+}) can participate in the stabilization of membranes. Zinc is known to facilitate the isolation of intact plasma membranes; it can inhibit the spontaneous hemolysis of erythrocytes when given orally to rats; and, finally, zinc inhibits in vitro the release of enzymes from lysosomes obtained from rat liver. In addition, the zinc ion can strongly inhibit cathepsin B, an acid protease which can catalyze the formation of bradykinin from kininogen. We found that zinc chloride at a dose of 0.40 mg per mouse effectively protects against lethality induced by endotoxin as measured by mortality at 24 hr.

It is becoming increasingly evident that lysosome disruption resulting in the release of harmful mediators such as proteases may be a major event in endotoxemia. Therefore, the application of agents such as zinc designed to stabilize lysosomes and/or inhibit lysosomal protease could prove useful in the treatment of endotoxemia and in the development of a better understanding of the means by which endotoxin induces shock.

46. Haemodynamic effects of different corticosteroids in controlled haemorrhagic shock in the dog. A. Hellman, E. Haggendal, M. Lindfors and D. Lundberg. Acta Anaesth. Scand. 22: 314-322, 1978.

The haemodynamic effects of massive doses of hydrocortisone (80-320 $mg \cdot kg^{-1}$), methylprednisolone (4-32 $mg \cdot kg^{-1}$), betamethasone (1.6-12.8 $mg \cdot kg^{-1}$) and aldosterone (0.1-0.8 $mg \cdot kg^{-1}$) and the interaction with phenoxybenzamine and propranolol have been studied during controlled haemorrhagic shock in the anaesthetized dog. Hydrocortisone was the only steroid which showed any significant vasodilating ability when given alone. The alpha-receptor blocking agent phenoxybenzamine distinctly decreased the total peripheral resistance. The effect of the phenoxybenzamine was increased in combination with hydrocortisone or methylprednsiolone, especially if the steroid was given as the first drug. The vasodilation found was efficiently abolished by the beta-receptor blocking agent propranolol. The ability of hydrocortisone or methylprednisolone to potentiate phenoxybenzamine was not shared by betamethasone or aldosterone. Thus, the haemodynamic effect of the steroid does not seem to be correlated to either a glucocorticoid nor a mineralocorticoid effect. It is suggested that the steroid effect studied is related to the ability of hydrocortisone or methylprednisolone to block the extra neuronal amine uptake which decreases the rate of elimination of the sympathetic transmitter from the vicinity of the adrenergic receptor of the vascular smooth muscles.

47. The effects of hemorrhagic shock on the diastolic properties of the left ventricle in the conscious dog. D. Alyono, W. S. Ring, and R. W. Anderson. Surgery 83: 691-698, 1978.

Although the depressed left ventricular (LV) performance and elevated filling pressure frequently observed following resuscitation from hemorrhagic shock (HS) usually have been attributed to impaired contractile function, the same findings could be explained by a loss of ventricular compliance. To determine the effects of HS on diastolic mechanics, the normalized LV diastolic pressure-dimension (P-D) relationship was studied in 10 chronically instrumented conscious dogs. Minor axis circumference (C) was obtained from ultrasonic dimension measurements of the external minor axis diameter (D). Circumferential strain (ε_C) was calculated from C, normalized to the unstressed circumference (C_O) obtained at zero transmural pressure (P_{TM}) during a transient vena caval occlusion. To minimize viscous effects, the static diastolic P-D relationship was determined by fitting only diastatic points ($D\varepsilon_C/DT = 0 \pm 0.03\ sec^{-1}$) to the equation $P_{TM} = \alpha(\varepsilon^{\beta\varepsilon_c}-1)$ where α and β are calculated elastic constants. After study in the control state, each dog was subjected to 2 hr of HS (mean arterial pressure = 40 mmHg), followed by reinfusion of all shed blood. In all 10 dogs the P-D curve immediately after reinfusion demonstrated a shift to the left, indicating a loss of ventricular compliance. C_O remained unchanged (15.4±9.8 cm control vs 16.5±0.9 cm immediately after HS), indicating that the shift did not represent a change in the unstressed circumference. Five survivors each displayed a progressive return of compliance to control during the 4 day study period. However, five nonsurvivors all demonstrated a progressive loss of compliance prior to

death. These results indicate that HS results in a progressive potentially reversible loss of ventricular compliance. This may explain the observation of depressed ventricular performance with normal or increased contractile function in HS.

48. Chemotaxis of human polymorphonuclears in vitro. V. Role of the non-segmented neutrophils and of the experimental conditions in the impairment of chemotaxis observed during bacterial infections. P. C. Frei, A. Hermanovicz and A. Pecoud. J. Lab. Clin. Med. 92: 577-583, 1978.

A few isolated cases of defective chemotaxis of PMNs have been reported; in some, this deficiency was considered to be responsible for recurrent infections. The cause-and-effect relation between infection and impaired chemotaxis is not evident in all these observations, and it is possible that defective chemotaxis might be a consequence rather than a cause of infection. Besides, the chemotactic activity of neutrophils during infections is still a matter of controversy; a reduction in chemotactic activity of neutrophils has been described in infected patients. Others have found a hyperactive neutrophil chemotactic response.

Chemotaxis of human leukocytes was studied in vitro with a microfilter having pores of 3 μm used as a substrate for the gradient. Under these conditions, nonsegmented neutrophils did not reach the compartment filled with the attractant, but a significant proportion of them did so when filters with larger pores were substituted. When leukocytes from infected patients were tested with the usual 3 μm pore filters, chemotaxis was reduced (as previously shown), but less markedly and less frequently in simultaneous experiments with larger pores. In experiments performed under agarose layers instead of filters, non-segmented neutrophils responded normally to chemoattraction, again suggesting that their impaired migration in filter experiments was a matter of pore size. When leukocytes from infected patients were assayed under aragose, no impairment occurred; on the contrary, a slight increase in both chemotaxis and random motility was observed. It was therefore concluded that some published cases of impaired neutrophil chemotaxis in infection might be due to technical bias related to pore size.

49. Comparison of the histamine hypersensitivity and the Limulus ameobocyte lysate tests for endotoxin activity. J. J. Munoz, R. K. Bergman, and K. E. Robbins. Infect. Immun. 22: 292-294, 1978.

The histamine hypersensitivity test and the Limulus amoebocyte lysate test were compared for their effectiveness to quantitate endotoxin activity. The two tests compared favorably in all the trials, except with a sample of endotoxin from Brucella abortus that gave a positive Limulus amoebocyte lysate test at a concentraction of 0.001 μg, while failing to sensitize mice to histamine at a dose of 16 μg per mouse. The Limulus amoebocyte lysate test was more sensitive than the histamine hypersensitivity test.

50. Hemodilution causes decreased compliance in puppies. C. Mavroudis and P. A. Ebert. Circulation 58 (Part II): I155-I159, 1978.

Cardiopulmonary bypass and hemodilution in the newborn have been associated with increased myocardial edema, which may be due to immature connective tissue formation. Five adult and four puppy dogs were placed on bypass while compliance and ventricular function (intraventricular balloon) were measured during normohemoconcentration (NH) (hematocrit 45.1, osmolality 307) and hemodilution with normal saline (hematocrit 24.7, osmolality 307). Compared with NH, the adult group showed no change in compliance or function after 90 min of hemodilution. The puppy group showed a marked decrease in compliance with hemodilution compared to NH ($p<0.001$ without change in ventricular function when peak systolic pressure was plotted against end-diastolic volume). Electron micrographs confirmed greater edema formation in the puppy group than the adult group with hemodilution. These changes demonstrate that the newborn heart is more sensitive to edema formation than the adult during hemodilution and that filling pressures do not necessarily reflect ventricular performance during the early post-perfusion period when compliance is decreased.

51. Model for disseminated intravascular coagulation: bacterial sepsis in rhesus monkeys. D. A. Wing, T. Yamada, H. B. Hawley, and G. W. Pettit. J. Lab. Clin. Med. 92: 239-251, 1978.

DIC is a hemorrhagic syndrome frequently encountered as a complication in severe gram-negative bacterial sepsis. An animal model for sepsis-associated DIC was developed in order to permit study of the appearance and development of this syndrome in relation to the entire disease process. Rhesus monkeys (4 to 6 kg) were infected by intravenous injection of 10^9 Salmonella typhimurium organisms and studied for a period of 7 to 10 days following infection. Ten of 23 infected monkeys developed petechial rash characteristic of DIC, which appeared on days 1 to 2 of infection and lasted 4 to 5 days. In the group of monkeys developing rash, activation of coagulation was suggested by an 80% decrease in platelet count and 20-30% increases in PT and APTT. Fibrinolytic system activation was indicated by the appearance of FDP. Kinin system activation was evidenced by decreases in both prekallikrein and kininogen. Changes in laboratory tests suggestive of subclinical DIC were also noted in infected monkeys which did not develop a rash. Pathologic evidence of DIC was obtained through observation of numerous fibrin thrombi in the kidneys of the only monkey which died in the course of infection. Occurrence of DIC in association with this experimental infection in rhesus monkeys was established on the basis of clinical, laboratory and pathologic criteria. Expression of the syndrome on days 1 to 2 following infection correlated with the period of increasing bacteremia.

52. Gluconeogenesis from alanine in endotoxin-treated dogs. R. E. Kuttner and J. J. Spitzer. J. Surg. Res. 25: 166-173, 1978.

Gluconeogenesis from alanine was studied in fasted, anesthetized, E. coli endotoxin-treated dogs by continuous infusion of L-[U-^{14}C]alanine. A marked increase in plasma alanine occurred following endotoxin. Alanine turnover remained unchanged. The fraction of glucose carbon derived from alanine was 9% at 4 hr after endotoxin, a threefold increase over

control dog values. Incorporation of carbon-14 label into plasma protein was depressed in experimental animals over 40% at the same time period. The data suggest that, in early endotoxemia, gluconeogenesis from alanine may actually increase.

53. Disseminated intravascular coagulation: a review. P. J. Hamilton, A. L. Stalker, and A. S. Douglas. J. Clin. Pathol. 31: 609-619, 1978.

Widely differing diseases offering no obvious threat to haemostasis are occasionally associated with inappropriate activation of the coagulation mechanism. When such a reaction is focal and involves a large vessel thrombosis ensues. Sometimes a more diffuse or disseminated intravascular coagulation is encountered. This affects predominantly the microcirculation and causes deposition of derivatives of fibrinogen in arterioles, capillaries, and venules. Disseminated intravascular coagulation is a secondary phenomenon, an intermediary mechanism of disease.

Some of the disease processes and clinical conditions associated with DIC:

Disease category	Example
Congenital abnormality	Cavernous haemangioma, hyaline pulmonary disease of newborn
Injury	Trauma, drowning, heat stroke, burns, envenomation
Infection	Bacterial, viral, rickettsial, protozoal (eg, malaria)
Immunological	Incompatible blood transfusion, allograft rejection, anaphylactic drug reactions, immune complex disease
Neoplastic	Leukaemia, solid tumours
Metabolic/endocrine	Diabetic ketoacidosis, acute fatty liver of pregnancy
Circulatory	Shock, pulmonary embolism, dissecting aneurysm, cyanotic heart disease
Obstetric	Amniotic fluid embolism, abruptio placenta, retained dead fetus

54. Insulin therapy for depressed myocardial contractility after prolonged ischemia. J. E. Muller, S. Mochizuki, J. K. Koster, Jr., J. J. Collins, Jr., L. H. Cohn, and J. R. Neely. Am. J. Cardiol. 41: 1215-1221, 1978.

Insulin was administered to two patients whose diminished myocardial contractility made it difficult to terminate cardiopulmonary bypass. In both instances, bypass was successfully terminated shortly after the insulin injection. These clinical observations led to experiments under the controlled conditions provided by the isolated, working rat heart preparation. The recovery of contractility after 30 min of severe ischemia was assessed in all 11 control and 11 insulin-treated hearts. Myocardial performance, as judged by the product of heart rate and peak systolic blood pressure, was significantly greater in the insulin-treated hearts. These clinical observations and experimental findings suggest the need for more extensive study of the potential value of insulin in treating depressed contractility after prolonged myocardial ischemia.

55. Antibiotic concentration in human wound fluid after intravenous administration. D. H. Bagley, J. MacLowry, R. M. Beazley, C. Gorschboth, and A. S. Ketcham. Ann. Surg. 188: 202-208, 1978.

Since the wound is the most common focus of infection in the surgical patient, adequate levels of antibiotic within the wound are essential. This study examines the concentrations of antibiotic achieved in human wounds. Fluid was collected at timed intervals on the first postoperative day from the wounds of 56 patients receiving antibiotics after regional lymph node dissection. Antibiotic concentration was determined by bioassay. Six antibiotics were studied: cephalothin, cefazolin, cephapirin, oxacillin, ampicillin and clindamycin. The cephalosporins and penicillins showed similar patterns of appearance in the wound fluid. The peak level occurred early (1-1 1/2 hours) with subsequent slow decrease. Clindamycin produced nearly constant levels in wound fluid. The concentration of each antibiotic in wound fluid surpassed the serum levels after 2.5 hours. At the dosages studied each antibiotic produced wound fluid concentrations greater than the MIC for most susceptible organisms. Higher doses provided higher wound fluid levels. The rate of appearance and the levels achieved should be considered in the choice of antibiotics in the surgical subject.

56. Optimal hematocrit value in critically ill postoperative patients. L. S. C. Czer and W. C. Shoemaker. Surg. Gynec. Obstet. 147: 363-368, 1978.

Falling hematocrit values are traditionally used to observe the course of active bleeding, since hematocrit values usually reflect acute blood losses. However, evidence from the literature suggests that, after volume replacement, some degree of normovolemic hemodilution may be desirable and that return to normal hematocrit values is not necessarily the appropriate goal of transfusion therapy. The optimal hematocrit value was defined empirically by three methods in a series of 94 critically ill postoperative patients. First, the mortality rates of postoperative patients were lowest with hematocrit values between 27 and 33%. Second, mortality rates were examined when both hematocrit values and the important cardiorespiratory variables were reduced; significantly increased mortalities occurred when hematocrit values were less than an average of 32%. Finally, oxygen availability and oxygen consumption increased significantly after whole blood and packed red cell transfusions were given when hematocrit values were less than 32% but not above 33%. When accurate blood volume measurements are not available, hematocrit values of 32% are optimal; when volume therapy is indicated, blood may be given with hematocrit values less than 32%, crystalloids or colloids are preferred with hematocrit values greater than 32%.

57. Acute respiratory distress syndrome and disseminated intravascular coagulation. R. M. Hardaway III. South. Med. J. 71: 596-598, 1978.

DIC appears to be a cause of the most severe type of shock lung, though other causes of respiratory distress are more common. One case of respiratory distress appears to have been helped by fibrinolysin, possibly by lysis of microclots in the pulmonary microcirculation, and its early administration may prove to be an adjunct to therapy in cases of DIC.

Why do some patients in shock develop respiratory failure and others not? And why do some patients in respiratory failure develop it in a shock situation and others not? Many causes of acute respiratory failure may or may not occur in a shock situation. Some of these are:

(1) Overtransfusion or infusion, with development of pulmonary edema.
(2) Left ventricular failure, with development of pulmonary edema.
(3) Low osmolality of blood, causing pulmonary edema.
(4) Normal or high blood osomolality, with capillary leakage into lungs and impedance of resorption.
(5) Direct trauma to the lungs or inhalation of toxic gases or liquids, especially vomitus.
(6) Fat and tissue embolism secondary to trauma or other causes.
(7) Transfusion embolism of small blood clots.
(8) Oxygen toxicity.
(9) Infection of the lung; bacterial pneumonia.
(10) Atelectasis due to bronchial obstruction or loss of surfactant.
(11) Lung damage due to respirator. Improper technic or care of intubation or tracheotomy may be detrimental.
(12) Other factors, such as pulmonary vascular constriction, antidiurectic hormone.

58. The role of coagulation system in the cytotoxicity of the bone marrow reactions by endotoxin. M. Hirata, M. Yoshida, K. Inada, and S. Yaegashi. Japan. J. Med. Sci. Biol. 31: 184-188, 1978.

It was shown that endotoxin made the lysosomal membrane labile and the eventual lysosomal enzymes release resulted in cytoxicity. The participation of lysosomal enzymes in the cytotoxicity was also suggested. The cytotoxicity was also produced in strain A mice which are defective in the complement 5 component. Endotoxin activates an alternative complement pathway as well as the classical pathway, and furthermore aggregates the platelets. Therefore, several factors, such as lysosomal enzymes, coagulation, complement, and platelets aggregation, would participate in manifestation of in vivo cytotoxicity caused by endotoxin. In vitro analysis of the cytotoxicity is now under investigation.

In the present study, it was confirmed that mouse fibrinogen and FDP react to antihuman fibrinogen. By the FDPL test, it was possible to determine the blood fibrinogen and FDP levels in mice. It was found that the blood FDP levels were increased after endotoxin injection and this findings supports an earlier report which stated that endotoxin was able to activate coagulation and fibrinolysis.

59. Effects of certain cations (Fe, Zn, Mg, and Ca) on bacterial endotoxins. J. Sourek, M. Tichy, and J. Levin. Infect. Immun. 21: 648-654, 1978.

The natural occurrence of cations Fe, Zn, Mg, and Ca in the lipopolysaccharide (LPS) of both the S and R forms of Shigella dysenteriae 1 was studied. LPS preparations were obtained either by phenol-water extraction or by extraction of cells with hypertonic sodium chloride-sodium citrate, with subsequent chromatographic purification on Sephadex G200 and Sepharose 4B columns. The cation in highest concentration in the Westphal extract was Mg^{2+} and the lowest one was Fe. In LPS of the Raynaud type, the cation in highest concentration was Ca^{2+}, and the lowest one was Fe. The effects of increasing and decreasing the concentrations of cations (Fe, Zn, Mg, Ca) upon the biological activity of the endotoxins was evaluated by using toxicity in mice and the Limulus test. It appeared that increased concentrations of Fe decreased

the toxicity of the R form of LPS, whereas Mg^{2+} decreased the toxicity of the S form. After prolonged dialysis of LPS preparations against deionized water, there was no consistent relationship between toxicity as determined in white mice and with the Limulus test.

60. Ionized hypocalcemia in critically ill patients with sepsis. B. Taylor, W. J. Sibbald, M. W. Edmonds, R. L. Holliday, and C. Williams. Canad. J. Surg. 21: 429-433, 1978.

Ionized and total hypocalcemia exist in critically ill patients with sepsis and the low value for Ca^T is secondary to hypoalbuminea. Low Ca^{2+} concentrations may result from relative hypoparathyroidism, due either to "resetting" of the glands to lower concentrations of Ca^{2+} or to inability of the glands to secrete appropriate amounts of PTH in the presence of sepsis. The therapy of hypocalcemia in critically ill patients depends upon the clinical situation. Patients with fulminant septicemia or those receiving large amounts of citrated blood will have a marked decrease in the Ca^{2+} value and should immediately be given free calcium supplements intravenously. Patients with sepsis who are critically ill but whose condition is more stable require a number of therapeutic procedures: removal of the septic focus, introduction of hyperalimentation to reverse the protein catabolism and administration of free calcium supplements to raise the Ca^{2+} concentration. We are currently assessing the hemodynamic response of these patients to calcium infusion to determine the importance of ionized hypocalcemia.

61. Influence of endotoxin on myocardial calcium transport and the effect of augmented venous return. M. E. Soulsby, F. D. Bruni, T. J. Looney, and M. L. Hess. Circ. Shock 5: 23-34, 1978.

The influence of endotoxin shock and of experimentally increased venous return during endotoxin shock on myocardial vesicular calcium uptake and calcium stimulated ATPase activity was investigated. Vesicular calcium uptake was depressed ($p<0.01$) from 0.9 μmoles/mg protein/min to 0.3 μmoles/mg/min after 5 hr of endotoxin shock. Control ATPase did not differ between endocardial surface and epicardial surface. This was accompanied by a depressed ($p<0.01$) ATPase activity from 0.2 μmoles P_i/mg/min to 0.6 μmoles P_i/mg/min at the endocardial surface, and to 0.9 μmoles P_i/mg/min at the epicardial surface. A femoral arteriovenous shunt was used to increase venous return by 313±71 ml/min (∿17 ml/kg) during the shock period. Vesicles from AV shunted animals after endotoxin were capable of normal calcium uptake and normal ATPase activity. Results suggest that myocardial depression during endotoxin shock is more severe on the endocardial surface and is caused by depressed vesicular calcium uptake secondary to depressed ATPase activity. Furthermore, this depression may be avoided by maintenance of an adequate venous return.

62. Cardiac and pulmonary function in regional intestinal shock. U. Haglund, H. Myrvold, and O. Lundgren. Arch. Surg. 113: 963-969, 1978.

After a 2-hr period of regional intestinal shock (arterial inflow pressure 30 to 35 mmHg; electrical stimulation of regional vasoconstrictor fibers at 6 Hz) a pronounced cardiovascular derangement is observed as

reflected in a rapid fall in arterial blood pressure. In this study, central hemodynamics and lung function were investigated to elucidate if functional changes in the thoracic organs might explain the cardiovascular collapse. No alteration of pulmonary function was observed. A negative inotropic influence on the heart was, however, noted as judged by a decreased left ventricular stroke volume and left ventricular maximal pressure change in the face of an increased left ventricular end diastolic pressure. Based on earlier observations with the same shock model, it is proposed that the cardiac effects were caused by cardiotoxic material released from the hypoxic gut.

63. Total and regional cerebral hemodynamic and metabolic abnormalities during endotoxin shock: prevention with methylprednisolone. T. E. Emerson, Jr. Adv. Neurol 20: 173-181, 1978.

The underlying mechanism of death during gram-negative septic or endotoxin shock has eluded clear definition, although a number of hypotheses have been advanced and a number of so-called "target organs" described. However, no hypothesis has been verified experimentally, and no "target organ" has been confirmed as being responsible for initiating irreversibility. The present study summarizes some of our earlier data and presents current findings relevant to cerebral hemodynamic and metabolic disorders during endotoxin shock and their prevention by pre- and posttreatment with the steroid methylprednisolone and plasma volume expanders. Since a number of investigators have shown it to be beneficial during circulatory shock, we chose to determine if this steroid would alter the cerebral hemodynamic and metabolic disorders normally associated with endotoxin shock, which might provide information relative to the mechanism by which methylprednisolone protects during shock states. As is seen herein, methylprednisolone does in fact prevent or ameliorate most of the cerebral hemodynamic disorders as well as preventing all of the measured cerebral metabolic disorders which normally occur in the dog shock model.

64. Escherichia coli bacteremia in patients with malignant diseases. W. E. Grose, V. Rodriguez, G. Norek, M. Luna, and G. P. Bodey. Arch. Int. Med. 138: 1230-1233, 1978.

Of 142 episodes of Escherichia coli bacteremia that were reviewed, appropriate antibiotics were administered during 98 episodes diagnosed premortem and 74 episodes (71%) responded. The highest cure rates were observed when the portals of entry were the urinary tract and soft tissues. Administration of adrenal corticosteroids did not affect the outcome of these patients. The patients' neutrophil counts at the onset and during infection were important factors in predicting survival. Septic shock occurred in 13% of all episodes, and only 11% of these patients responded. Of those patients who died, 63% died within the first 24 hours. Aminoglycosides, cephalosporins, and semisynthetic penicillins used alone or in combination offered optimal coverage.

65. Endotoxin and the liver. III. Modification of acute carbon tetrachloride injury by polymyxin B--an antiendotoxin. J. P. Nolan, and L. I. Leibowitz. Gastroenterology 75: 445-449, 1978.

Previous work suggests that endotoxin of enteric origin may contribute to both acute and chronic liver injury by other agents. In particular, evidence exists that endotoxin tolerance modifies biochemical and histological evidence of carbon tetrachloride hepatotoxicity. The present study was undertaken to ascertain whether another method of modifying endotoxicity would protect against carbon tetrachloride (CCl_4) damage as well. The antibiotic polymyxin B (PB) has unique antiendotoxin properties not shared by gentamicin sulfate, an antibiotic with a similar antibacterial spectrum. In groups of rats pretreated with either PB, gentamicin, or diluent, the LD_{100} of an oral dose of CCl_4 was reduced by PB to an LD_{50}, but the gentamicin pretreatment was without effect. When a sublethal dose of CCl_4 was administered, both the SGOT and SGPT values were significantly lower in the PB group of rats. This biochemical protection was mirrored in the striking lack of histological liver necrosis in these animals, protection not shared by the gentamicin group or controls. The incidence of endotoxemia 24 hr after CCl_4 as detected by lead acetate enhancement was also reduced by PB pretreatment. These findings further support the contention that endotoxins from the gut may be major contributors to the extent of liver injury induced by an unrelated toxin.

66. Effects of acute endotoxemia and glucose administration on circulating leukocyte populations in normal and diabetic subjects. H. S. Gilbert, E. J. Rayfield, H. Smith, Jr., and G. T. Keusch. Metabolism 27: 889-899, 1978.

Effects of intravenous endotoxin and glucose administration on circulating leukocyte populations were compared in seven normal subjects and seven patients with juvenile-onset diabetes by means of automated cytochemical differential counting to quantitate each cell type. Both groups had comparable control cell counts that were unaffected by glucose tolerance testing but altered significantly by endotoxin. Different patterns of response to endotoxin were observed for different circulating cell types. The response of diabetics was parallel to that of normals but showed lower neutrophil and monocyte rebound, longer lasting depression of lymphocytes and eosinophils, and greater rebound of basophils on the day following endotoxin exposure. Characterization of distinctive normal response patterns of circulating leukocyte populations to endotoxin and comparison with responses in diabetics revealed abnormalities under conditions of stress that may impair the diabetic's ability to cope with acute infection.

67. Relationship between the plasma glucose level and glucose uptake in the conscious dog. A. D. Cherrington, P. E. Williams, and M. S. Harris. Metabolism 27: 787-791, 1978.

In the absence of a change in the pancreatic hormonal milieu, elevations in the normal fasting plasma glucose level have little effect on glucose clearance. In view of these data, and the previously established responsiveness of M to hormones, glucose clearance can be considered to represent a useful index of hormone action on glucose uptake in vivo. Care should be taken, however, when interpreting clearance data obtained under hypoglycemic conditions, since there is a possibility that clearance may spontaneously increase at very low plasma glucose levels.

68. Host defense against opportunist microorganisms following trauma. II. Changes in complement and immunoglobulins in patients with abdominal trauma and in septic patients without trauma. A. B. Bjornson, W. A. Altemeier, H. S. Bjornson. Ann. Surg. 188: 102-108, 1978.

Total hemolytic complement (CH_{50}), conversion of C3 by inulin and cobra venom factor (CoVF), and immunochemical levels of C1q, C4, C2, C3, C5, factor B, properdin, C3b inactivator (KAF), and immunoglobulins (Igs) G, A, and M were measured in the sera of ten patients with abdominal trauma and ten medical patients with septicemia without trauma. Reduction in C3 conversion by CoVF and decrease in the levels of properdin and KAF were demonstrated in the trauma sera. CH_{50} and the level of C5 were also decreased. Conversion of C3 by inulin and levels of factor B, C1q, C4, C2, and C3 were found to be normal in the patients' sera. Complement levels and activities were found to be normal in the sera of the septic non-trauma patients. A decrease in serum IgM was observed in both patient groups; levels of IgG and IgA were normal. These results indicated that abnormalities of immunoglobulin and of the alternative and classicial complement pathways were associated with nonburn trauma. Moreover, the data suggested that consumption of the classicial complement pathway associated with septicemia in the thermally injured patient resulted from synergism between the trauma and infection rather than from septicemia per se.

69. Effects of endotoxin on the pregnant baboon and fetus. H. O. Morishima, W. H. Niemann, and L. S. James. Am. J. Obstet. Gynec. 131: 899-902, 1978.

Effects of E. coli endotoxin upon uterine activity and maternal and fetal condition were studied in four pregnant baboons and their fetuses. Uterine activity increased significantly following administration of endotoxin to the mother. Endotoxin also produced maternal circulatory collapse, severe acidosis, and profound fetal asphyxia resulting in death. Death also occurred in three of the four mothers within 24 hours without amelioration of their conditions.

70. Management of shock following acute myocardial infarction. Part II. Mechanical circulatory assistance. L. A. Kuhn. Am. Heart J. 95: 787-795, 1978.

Intraaortic balloon pumping may provide temporary hemodynamic benefit in acute myocardial infarction with shock but reports have differed rather widely concerning its efficacy in providing long-term survival. Much of this variation depends on differing criteria for the definition of "shock". The intraoartic balloon is of considerable efficacy in stabilizing the patient with a surgically remediable cause for the shock syndrome, such as ruptured interventricular septum or massive mitral regurgitation. Survival rate is low even with the intraaortic balloon when shock is present in the absence of such conditions, although there may be slight additional salvage with emergency revascularization and/or infarctectomy and aneurysmectomy. Because of the poor results with all modalities of treatment once the shock syndrome is apparent, attention should be directed to attempts to prevent shock and to other means of circulatory support. It is not known whether shock can be prevented but use of the intraaortic balloon pump in poor risk patients who are not in shock as determined by hemodynamic measurements should be studied intensively for this purpose.

71. Hepatic oxygen supply and plasma lactate and glucose in endotoxic shock. R. D. Rink, B. L. Short, and C. Pennington. Circ. Shock 5: 105-113, 1978.

Hepatic oxygen supply and selected blood parameters were recorded in fasted male rats given 20-30 mg/kg Escherichia coli endotoxin i.p. Mortality was 70% within 24 hr. Measurements during the initial 8 hr postendotoxin recorded no differences of hematocrit, systemic arterial pressure, or arterial pO_2 between survivors and eventual nonsurvivors. However, by the sixth or eighth hour nonsurvivors showed significantly higher plasma lactate, lower plasma glucose and blood pH, and a greater degree of hypocapnea. In addition, mean hepatic pO_2 had decreased from 25.2 mmHg during the control to 3.8 mmHg after 6 hr. A decline of hepatic oxygen supply also occurred in surviving rats but was significantly less severe. Control rats showed a mild degree of respiratory alkalosis but were otherwise stable over 8 hr. The relationship of hepatic oxygen supply to differences of plasma lactate and glucose is discussed. Failure of hepatic circulation is cited as the probable cause of extensive liver anoxia and related developments in nonsurviving endotoxic rats.

72. Comparison of the cytotoxic actions of hypoxia and endotoxin in the perfused cat liver. A. M. Lefer and M. J. Galvin. Circ. Shock 5: 145-155, 1978.

The isolated cat liver perfused at a constant flow with Krebs-Henseleit solution containing low molecular-weight dextran was employed to ascertain the direct effects of hypoxia or endotoxin on hepatic integrity. Hypoxia resulted in large increases in circulating lactate dehydrogenase (LDH) activity and in amino-nitrogen concentration, whereas endotoxin at a dose of 0.75 μg/gm liver wet weight resulted in only small changes in these variables after 150 min of perfusion. Perfusion pressure and perfusate pH did not change significantly in response to either intervention. Both hypoxia and endotoxin significantly compromised lysosomal stability as evidenced by large increases in circulating levels of cathepsin D, large increases in the nonsedimentable fraction of tissue cathepsin D (ie,

increased percentage of free activity), and changes in the ultrastructural appearance of liver lysosomes associated with enhanced fragility (eg, swelling, increased vacuolization). Both interventions also significantly impaired phagocytosis by reticuloendothelial cells within the liver. However, neither intervention altered BSP clearance, indicative of a lack of effect on parenchymal cell clearance. These findings indicate that both endotoxin and hypoxia induce direct cellular damage within the liver; however, endotoxin exerted a more selective action on lysosomes, whereas hypoxia produced more of a diffuse cytotoxic effect.

73. Increased template activity of chromatin isolated from shocked liver. C. T. Warnick and H. M. Lazarus. Circ. Shock 5: 157-161, 1978.

Hemorrhagic shock causes an increase in the template activity of chromatin isolated from rat liver, as measured with E. coli RNA polymerase. The increase in template activity is directly related to the time of shock: The longer the shock period, the greater the increase in template activity. Reinfusion reduces the increased template activity. The increased template activity of the chromatin during hemorrhagic shock may be indicative of nuclear changes which contribute to the inability of the cell to recover from severe shock.

74. Regional glucose metabolism in the cat kidney in vivo. P. A. Friedman and J. Torretti. Am. J. Physiol. 234: F415-F423, 1978.

Glucose metabolism in the areas of superficial (purely cortical) and deep (cortical and medullary) venous drainage in the cat kidney was studied. Deep and superficial renal venous minus arterial (RV-A) concentration differences of glucose, lactate and the nonmetabolizable amino acid, cycloleucine, were measured using protein concentration to correct for water gain or loss. In addition, the synthesis of glucose, lactate, and CO_2 from radioactive precursors was observed. $(RV-A)_{glucose}$ was positive in the superficial and negative in the deep venous drainage areas. Such difference was not observed with the nonmetabolizable amino acid. The foregoing suggests that the results with glucose are reflections of metabolic differences between the two areas and are not entirely attributable to reabsorption in the superficial area of glucose filtered in the deep area. Both regions exhibited net uptake of lactate. Synthesis of radioactive glucose during the intrarenal infusion of labeled lactate (and α-ketoglutarate) occurred in both the deep and superficial areas. Synthesis of radioactive lactate from labeled glucose was also observed for both areas. Since the superficial drainage area represents cortex only, it is concluded that both glycolysis and gluconeogenesis occur in renal cortex. The net gain of chemical glucose across the superficial drainage area indicates that the rate of gluconeogenesis exceeds the rate of glycolysis. We speculate that the net loss of glucose across the deep drainage area (deep cortex and medulla) results, in part, from glycosis in the medulla.

75. Purification of a fibrinolysis inhibitor in serum from post-traumatic patients. L. Bagge, I. Björk, T. Saldeen, and R. Wallin. Thrombos. Haemostas. 39: 97-100, 1978.

A fibrinolysis inhibitor was purified in serum from post-traumatic patients by the use of flat bed electrofocusing of serum desalted by gel chromatography followed by affininty chromatography on a column of matrix-linked plasminogen. Disc gel electrophoresis yielded one protein band. The inhibitor protein was also found in normal serum, but in a lower concentration.

76. Ionized calcium and magnesium in the baboon: Hemorrhagic shock and resuscitation. M. A. Carpenter, D. D. Trunkey, and J. Holcroft. Circ. Shock 5: 163-172, 1978.

Ionized calcium (Ca^{2+}) and ionized magnesium (Mg^{2+}) are important intracellular "second messengers" and control excitation-contraction coupling excitation-secretion coupling, oxidative phosphorylation, and mitochondrial acid-base balance. This study examines the effect of hemorrhagic shock on serum Ca^{2+} and Mg^{2+}. Eight baboons were subjected to severe hemorrhagic shock and then resuscitated. Ca^{2+} was measured by the Orion SS-20 flow-through calcium electrode and Mg^{2+} was calculated by the method of Killen. Other measurements included: total calcium, bound calcium, total magnesium, bound magnesium, albumin, globulin, total protein, phosphate, pH and hematocrit. This study shows that there are significant disturbances of Ca^{2+} and Mg^{2+} during resuscitation from hemorrhagic shock. These disturbances may in part explain cellular dysfunctions during shock, including decreased myocardial contractility, inappropraite secretion of endocrine cells, decrease in oxidative phosphorylation, and mitochondrial acidosis.

77. Influence of steroid structure in relation to liver metabolism during endotoxin lethality in mice. G. Lazar, S. Sekiya, and M. K. Agarwal. Exptl. Cell Biol. 45: 176-183, 1977.

The influence of a number of steroid molecules on hepatic metabolism was determined in relationship to their ability to alter endotoxin lethality in intact mice. Progesterone, testosterone, estradiol, pregnenolone-16-α-carbonitrile and spironolactone did not alter endotoxin lethality, liver glycogen or tryptophan pyrrolase (TP) levels; all these materials increased liver tyrosine transaminase (TT) levels most probably due to mediation by endogenously liberated glucocorticoid hormones. Aldosterone and deoxycorticosterone induced liver TP, TT and glycogen but did not protect against lethality. Cortisone, hydrocortisone, triamcinolone, dexamethasone and 9-α-fluorohydrocortisone protected against lethality, increased liver glycogen and TT, but only trimcinolone induced liver TP. Collectively, there was no clear relationship between the protective effect and the increase or decrease of a given liver process. These further emphasize the need to reconsider molecular mechanisms of endotoxic reactions.

78. Effects of endotoxin on carbohydrate metabolism in inbred mice. R. S. Roy, S. I. Vas and H. G. Robson. Can. J. Comp. Med. 40: 434-441, 1976.

Effects of endotoxin on carbohydrate metabolism were studied in A/HeJ (endotoxin-sensitive) and C3H/HeJ (endotoxin-resistant) inbred mice. A/HeJ developed hypoglycemia within 2 hr after endotoxin injection, yet liver glycogen content did not differ from controls. Similarly treated C3H/HeJ mice did not develop significant hypoglycemia. Administration of glucagon to endotoxin-treated A/HeJ mice failed to elevate their blood glucose concentrations, while endotoxin-treated mice of the same strain responded to dibutyryl cyclic AMP with a significant elevation of blood glucose. C3H/HeJ mice on the other hand responded to glucagon and dibutyryl cyclic AMP with elevated blood glucose. Endotoxin-treated C3H/HeJ mice but not A/HeJ mice were able to carry out gluconeogenesis induced by prednisolone, while both inbred strains showed active glycogenesis after administration of an exogenous glucose load. Administration of glucagon resulted in diminished liver glycogen concentrations in A/HeJ endotoxin-treated mice suggesting no impairment of glycogenolysis. The inability of endotoxin-treated A/HeJ mice to respond to glucagon could be due to impairment of gluconeogenesis. Although endotoxin interfered with the capacity of both inbred strains to respond to glucagon administration with elevation of liver cyclic AMP, the effect was significantly more severe in A/HeJ mice. The susceptibility of A/HeJ mice to the lethal effect of endotoxin may be related to the apparent sensitivity of carbohydrate metabolic pathways to disturbance by endotoxin.

79. Accion de la endotoxina del Escherichia coli sobre higado de cerdo aislado. J. A. R. Montes, I. Rossi, M. G. Noguera, A. Iglesias, J. L. Castillo-Olivares, and P. Escartin. Revista Clinica Espanola 148: 127-130, 1978.

The effect of E. coli endotoxin was studied on isolated pig liver. A decrease of bile flow was obtained in direct relationship to the dose of endotoxin administered. GOT significantly increased in the cases of less bile flow corresponding to the cases which received the highest amounts of endotoxin.

80. Effects of endotoxin on regional blood flow in the unanesthetized guinea pig. J. L. Ferguson, J. J. Spitzer, and H. I. Miller. J. Surg. Res. 25: 236-243, 1978.

Regional distribution of blood flow was determined using labeled microspheres in control and endotoxin-treated guinea pigs. In control animals, blood flow for all tissues and organs remained constant throughout the experiments. The endotoxin-treated guinea pigs that survived for 3 hr demonstrated an early depression in cardiac output and heart rate. With these cardiovascular effects there was a fractional redistribution of blood flow favoring hepatic artery, organs drained by the hepatic portal system, diaphragm, and adrenal glands. The brain, caecum, adipose tissue, heart, kidneys, and stomach did not have altered fractional flow but did demonstrate a reduced absolute blood flow. Blood flow was compromised to the spleen, pancreas, skin and skeletal muscle, due to both the reduced

cardiac output and a decrease in the fractional distribution. Guinea pigs that died early had an increased fractional blood flow to the heart and brain with no increase in distribution to the organs drained by the portal vein. The different responses of animals dying early from those living for at least 3 hr were probably a result of a more depressed cardiovascular system.

81. Blood coagulation changes in shock. P. Garcio-Barreno, J. L. Balibrea, and P. Aparicio. Surg. Gynec. Obstet. 147: 6-12, 1978.

A secondary coagulopathy develops in a state of hypovolemic shock; in endotoxin shock, the coagulopathy is primary. As the changes in the hemodynamic and metabolic functions advance in hypovolemic shock, a state of hypercoagulability appears which reinforces the irreversible nature of this condition. In endotoxin shock, a primary mixed coagulopathy develops as an event directly related to the presence of bacterial lipopolysaccharides. The first finding is the activation of the fibrinolytic system through the activation of the fibrinolytic system through the activation of the serum complement system by means of the participation of the properdin, the so-called alternate pathway to the complement system. At the same time and by an identical mechanism, the activation of Factors VII and XI occurs through the activation of the Fletchner Factor, while the Hageman trait is activated by kinogen. Immediately after and following an antigen-antibody type reaction, endotoxin stimulates activation of platelets in the presence of gamma-2-globulin along the classical pathway of activation of the serum complement.

82. Colloid osmotic and pulmonary wedge pressures in acute respiratory failure following hemorrhage. V. K. Puri, U. Freund, R. W. Carlson, and M. H. Weil. Surg. Gynec. Obstet. 147: 537-540, 1978.

Earlier observations reported from our center demonstrated a close relationship between pulmonary edema and a critical reduction in colloid osmotic pressure-pulmonary artery wedge pressure gradient to levels of less than 6 mmHg. It is apparent that elevation of left ventricular filling pressure or reduction in colloid osmotic pressure, when taken singly, does not explain the development of the syndrome of acute respiratory failure. However, the net effect of concurrent changes in colloid osmotic pressure and pulmonary artery wedge pressure may be an important issue, accounting for increases in extravascular lung water and the evolution of acute respiratory failure. Acute respiratory failure evolved in five patients following hypovolemic shock related to trauma or surgical operation, or both. A reduction in colloid osmotic pressure, increases in pulmonary artery wedge pressure and reductions in colloid osmotic pressure-pulmonary artery wedge pressure gradient to levels which are likely to account for pulmonary edema were observed. Accordingly, reduction in the colloid hydrostatic pressure gradient may, in part, explain the development of acute respiratory failure after acute blood loss. In one instance, however, the absence of such reduction in the colloid osmotic pressure-pulmonary artery wedge pressure gradient together with increases in pulmonary vascular resistance showed that colloid osmotic pressure and pulmonary artery wedge pressure are not exclusively operative in the pathogenesis of the clinical syndrome of acute respiratory failure.

83. Effect of dopamine on renal blood flow of baboon in endotoxin shock. P. S. Rao and B. Bhagat. Pflugers Arch. 374: 105-106, 1978.

Renal vasodilation observed in canine endotoxemia did not occur during endotoxin shock in the baboon: in fact, renal artery blood flow was markedly reduced. Infusion of dopamine in the baboon restored the renal artery blood flow.

84. Anti-endotoxin actions of methylprednisolone in the isolated perfused cat liver. M. J. Galvin, K. Shupe and A. M. Lefer. Pharmacology 17: 181-190, 1978.

The efficacy of the synthetic glucocorticoid, methylprednisolone, was examined in vitro using an isolated cat liver perfused with a blood-free medium. Addition of endotoxin (75μg/g tissue) to the perfusate did not change perfusion pressure or total oxygen consumption. However, cellular integrity was severely compromised as reflected by increases in perfusate lactate dehydrogenase and cathepsin D activities, increases in tissue lysosomal fragility, and enlargement and vacuolization of lysosomes. Addition of methylprednisolone ($1x10^{-3}$ M) to the perfusion medium prevented the endotoxin-induced changes in hepatocyte integrity. It is suggested that a major action of endotoxin in the liver is to increase lysosomal fragility, and the protective action of methylprednisolone appears to be related to its lysosomal stabilizing action. The potent anti-endotoxin action of glucocorticoids in vivo may be due in part to the stabilization of lysosomal membranes in tissues such as the liver.

85. The effects of bacterial endotoxins on host mediation systems. A review. D. C. Morrison and R. J. Ulevitch. Am. J. Path. 93: 526-617, 1978.

This review article summarizes the following topics:

1. Historical background
2. Composition of bacterial endotoxins
3. Relationship of endotoxin structure to biologic activity
4. Human mediation systems (serum complement, coagulation systems)
5. Cellular mediation systems (platelets, polymorphonuclear leukocytes, macrophage/monocyte-endotoxin interactions, endothelial cell-endotoxin interactions, mast cells/basophils)
6. Summary and conclusions

86. Alterations of plasmin activity, plasminogen levels and activity of antiplasmins during endotoxin shock in dogs. A. O. Aasen, M. J. Gallimore, K. Ohlsson, and E. Amundsen. Haemostasis 7: 164-169, 1978.

Spontaneous plasmin activity and fast-reacting and time-dependent antiplasmin activities were determined during various stages of canine endotoxin shock by means of assays utilizing a chromogenic tripeptide derivative. During shock, gradually decreasing values of both antiplasmins were found, revealing msot pronounced falls of fast-reacting antiplasmin. These changes of plasma antiplasmin activities were accompanied by decreasing values of plasminogen and evidence of plasmin activity. Immunochemical determination of plasma levels of α_2-macroglobulin (α_2-M) and α-antitrypsin (α_2-AT) and gel filtration studies, demonstrated marked falls in levels of α_2-M and α_2-plasmin inhibitor and small reductions of α_2-AT in this state.

87. Platelets in Sanarelli-Shwartzman reaction and in human sepsis. J. Hawiger. Platelets: A multidisciplinary approach. (Edited by G. de Gaetano and S. Garattini.) Raven Press, New York, 1978, pp. 321-8.

There are three essential elements of endotoxin interaction with platelets: (a) endotoxin, (b) platelets, and (c) plasma factors. In addition, other cell types such as granulocytes, mononuclear cells, and endothelial cells may mediate the effect of endotoxin upon platelets.

Recently obtained data have provided substantial support to the notion that human platelets are target cells for endotoxin. Human platelets possess endotoxin-binding component ("receptor"). Endotoxin receptor is probably a phospholipid and is responsible for selective release reaction from dense granules. However, the dose of endotoxin required for initiation of in vitro release reaction from human platelets is many times higher than the concentration of endotoxin eliciting fever and thrombocytopenia in normal human volunteers. The changes in human platelets induced by endotoxin in vivo (thrombocytopenia) or in vitro (serotonin release) are not suppressed by aspirin suggesting that endotoxin activates platelets through a pathway independent of prostaglandin endoperoxide biosynthesis.

88. The role of platelets, leukocytes, and complement in the activation of intravascular coagulation by endotoxin. G. Muller-Berghaus. Platelets: A multidisciplinary approach. (Edited by G. de Gaetano and S. Garattini.) Raven Press, New York, 1978, pp. 303-320.

Thrombocytopenia, leukocytopenia and hypocomplementemia are observed both in patients suffering from septic infections due to gram-negative bacteria and in animals after endotoxin administration. Platelets as well as leukocytes, erythrocytes and endothelial cells are target cells for endotoxin. It has been shown that erythrocytes, granulocytes, mononuclear leukocytes and platelets possess endotoxin-binding structures on their surfaces. Obviously, plasma constituents are not involved in the binding of endotoxin to the surface of these cells. Certain effects of endotoxin mediated by these cells, however, seem to depend on plasma factors as the activation of intravascular coagulation by endotoxin. The precise mechanism how endotoxin induces generalized intravascular coagulation leading to capillary microclots in various organs is not well understood. The complement system has been accused as one factor involved in the activation of intravascular coagulation as synchronic changes in the complement and coagulation systems are observed in patients suffering from generalized intravascular coagulation or in animals after endotoxin injection. In vitro studies have demonstrated endotoxin-induced activation of the complement system by way of the classical and/or the alternate pathways. The lipid A portion of endotoxin seems to be responsible for the classical pathway activation and the polysaccharide portion of endotoxin for the alternate pathway activation of complement.

89. Platelets and endotoxins: Complement-dependent and complement-independent interactions. N. Semeraro, M. Colucci, D. Fumarola, and J. Vermylen. Platelets: A multidisciplinary approach. (Edited by G. de Gaetano and S. Garattini.) Raven Press, New York, 1978, pp. 293-302.

Bacterial endotoxin (lipopolysaccharides, LPS) have a marked effect on the platelets of rabbits and other animals. Administration of endotoxins to rabbits leads to thrombocytopenia, platelet aggregates in the blood

vessels of several organs, appreciable amounts of serotonin in plasma and unmasking of platelet factor 3 (PF3). These in vivo effects have been confirmed in vitro by the observation that endotoxins aggregate rabbit platelets, induce release of vasoactive amines and adenine nucleotides and activate PF3.

There is substantial evidence that the rabbit platelet-endotoxin interaction is complement-dependent. Following complement activation by endotoxin and cleavage of C3, platelet aggregation occurs as a result of an immune-adherence phenomenon, subsequent fixation of the terminal components of complement leads to "bystander" lysis and activation of PF3. It has been suggested that, besides PF3, a tissue factor activity may be provided by the platelets through component -mediated "bystander" lysis which would activate the clotting system, at least in part, via the extrinsic pathway.

In conclusion LPS affect rabbit platelets via complement-dependent and complement-independent mechanisms, but act on human platelets only via the complement-independent pathway. Mucopeptides affect rabbit platelets only via the complement-mediated pathway and have no effect on human platelets.

90. Physiology of haemostasis. J. Vermylen. Platelets: A multidisciplinary approach. (Edited by G. de Gaetano and S. Garattini.) Raven Press, New York, 1978, pp. 3-16.

The aim of this review article is to provide a general background for the detailed discussion of specific aspects of platelet physiology during the symposium, "Platelets: A multidisciplinary approach". The following haemostatic processes are discussed: Vasoconstriction, platelet adhesion, formation of the platelet plug, reinforcement of the platelet plug with fibrin, and fibrinolysis.

91. Evidence of incomplete left ventricular relaxation in the dog. Prediction from the time constant for isovolumic pressure fall. M. L. Weisfeldt, J. W. Frederiksen, F. C. P. Yin, and J. L. Weiss. J. Clin. Invest. 62: 1296-1302, 1978.

Although it has been proposed that incomplete relaxation explains certain increases in left ventricular end diastolic pressure relative to volume, there has been no clear demonstration that incomplete relaxation occurs in the intact working ventricle. To identify incomplete relaxation, left ventricular pressure-dimension relationships were studied in 10 canine right heart bypass preparations during ventricular pacing. The fully relaxed, exponential diastolic pressure-dimension line for each ventricle was first determined from pressure and dimension values at the end of prolonged diastoles after interruption of pacing. For 167 beats during pacing under widely varying hemodynamic conditions, diastolic pressure-dimension values encountered this line defining the fully relaxed state during the filling period indicating that relaxation was complete before end diastole. The time constant for isovolumic exponential pressure fall (T) was determined for all beats. For this exponential function, if no diastolic filling occurred, 97% of pressure fall would be complete by 3.5 T after maximal negative dP/dt. For the 167 beats the fully relaxed pressure-dimension line was always encountered before 3.5 T.

With very rapid pacing rates (170-200 beats/min) and(or) with pharmacologic prolongation of relaxation, incomplete relaxation occurred as evidenced by the fact that the line defining the fully relaxed state was never reached during diastole (n=15). This evidence of incomplete relaxation occurred only when the subsequent beat began before 3.5 T but did not always occur under these conditions. Thus, an increase in end diastolic pressure relative to diastolic volume may result from incomplete relaxation under conditions of sufficiently rapid heart rate or sufficiently prolonged ventricular relaxation. Incomplete relaxation does not occur when the next beat begins more than 3.5 T after maximum negative dP/dt.

92. The significance of serum-sensitive bacilli in gram-negative bacteremia. B. Elgefors and S. Olling. Scand. J. Infect. Dis. 10: 203-207, 1978.

Clinical findings from 76 patients with gram-negative bacteremia were analyzed and related to the sensitivity of the blood isolated to the bactericidal activity of normal human serum. 28 strains (37%) were resistant, an equal number intermediately sensitive and 20 markedly sensitive (26%). No correlation was found between serum sensitivity and origin of the bacteremia, presence of fever or blood granulocyte count. The frequency of shock in immunocompromised patients with serum-resistant strains was 60%; in those with intermediately or markedly sensitive strains it was 44%. In the non-immunocompromised patients with resistant strains the frequency of shock was 33 vs 10% in those without such strains. Thus the risk of developing shock with gram-negative bacteremia seems to depend on both parasite and host factors, although in this study only the latter were statistically significant. We conclude that serum-sensitive strains can invade the blood stream in spite of the serum bactericidal activity and cause severe disease in some patients.

93. Portal and systemic bacteraemia and endotoxaemia in liver disease. D. R. Triger, T. D. Boyer, and J. Levin. Gut 19: 935-939, 1978.

Using a percutaneous transhepatic technique, blood was obtained from the portal veins of 30 patients with various hepatic disorders and examined for the presence of bacteria and endotoxin. Simultaneous samples also were drawn from hepatic and peripheral veins. In three cases, portal vein cultures grew diphtheroids, which were of doubtful significance, while all hepatic and peripheral cultures were sterile. Endotoxin was detected in 7 portal vein samples; in none of these patients were the hepatic or peripheral blood samples positive. In three cases, only peripheral blood samples were positive for endotoxin. It was concluded that portal bacteraemia occurs as infrequently in patients with liver disease as in those without. Portal endotoxaemia was detected in patients with all degrees of liver disease but, even in patients with moderately severe portal hypertension, the liver may remain an effective filter of endotoxin.

94. Effects of local thrombinaemia and endotoxinaemia on hepatic circulation in the anaesthetized dog. M. Hellgren, P. Olsson, and L. Thulin. Scand. J. Clin. Lab. Invest. 37: 77-84, 1977.

The acute response of the hepatic circulation to thrombonaemia and endotoxinaemia were investigated in the anaesthetized dog. Small amounts of thrombin were infused into the hepatic artery and portal vein. The effects of thrombin were compared to those of minor amounts of portally infused endotoxin. Portal pressure increased significantly following portal infusion of thrombin and endotoxin. Both substances decreased the blood flow markedly in the hepatic artery, while that in the superior mesenteric artery and portal vein decreased only slightly. Heparin and polyphlorethin phosphate abolished all effects of thrombin. Bradykinin infused simultaneously inhibited only the effect on the hepatic artery. Vasoactive intestinal peptide, which has the same vasodilatory effect in the liver, did not. It is believed that thrombin and perhaps endotoxin exert a vasoconstrictive effect mediated by products released from platelets.

95. Coagulation for cardiologists. S. Wessler and S. N. Gitel. Am. Heart J. 96: 811-823, 1978.

Vascular potency depends upon the balance between at least six subtly interrelated systems each of which, in itself, is exceedingly complex. These include the endothelium and its subjacent structures, the platelets, the coagulation and fibrinolytic systems, the inhibitors of these latter systems, and the flow characteristics of blood within the circulation. Alterations of the rather delicate balance among these hemostatic systems can result in serious hemorrhage or major thromboembolism. This is a discussion that focuses on the issue of thrombosis and its management.

96. Study of chemical sympathectomy in endotoxin-induced lethality and fibrin deposition. W. K. Bolton and N. O. Atuk. Kidney Internat. 13: 263-270, 1978.

Shock and the generalized Shwartzman reaction are well known features of endotoxin which have been shown to involve the sympathetic nervous system. The mechanism of sympathetic nervous system involvement with endotoxin injection was studied in rabbits chemically sympathectomized with 6-hydroxydopamine. Endotoxin, in doses producing a spectrum of morbidity and mortality in normal rabbits, was administered i.v. to chemically sympathectomized, normal, and unilateral renal surgically sympathectomized animals. Chemical sympathectomy produced a significant depletion of tissue norepinephrine which, in endotoxin recipient animals, was associated with a significantly lower mortality rate and greatly decreased fibrin deposition in the lungs and kidneys, despite intravascular coagulation. Unilateral renal sympathectomy afforded protection to the ipsilateral kidney, but data on mortality and systemic fibrin deposition were similar to those reported for normal rabbits given endotoxin. Six-hydroxydopamine prevents significant tissue injury secondary to endotoxin in this experimental model. In addition, the data provide direct evidence that an intact reactive sympathetic nervous system is essential for development of lethal toxicity and generalized Shwartzman reaction due to endotoxin.

97. Acidemia and insulin resistance in the diabetic ketoacidotic rat. C. Cuthbert and K.G.M.M. Alberti. Metabolism 27 (Suppl. 2): 1903-16, 1978.

Insulin sensitivity with respect to changes in blood glucose, lactate, and ketone body concentrations has been studied in normal and streptozotocin-diabetic rats. Insulin was infused at doses ranging from 0.03 to 100 U/kg/hr and dose response curves established. Maximal responsiveness was achieved at 1 U/kg/hr for glucose and 0.3 U/kg/hr for ketone bodies in normal rats. In diabetic rats, responsiveness and sensitivity were directly proportional to pH. When pH was less than 6.9, there was little or no response. Ammonium chloride administration to normal rats or to mildly acidotic diabetic rats caused almost total loss of responsiveness to insulin. The insulin insensitivity found in severely acidemic diabetic rats could be reversed by sodium bicarbonate administration. Liver and muscle metabolite patterns suggested that loss of responsiveness and sensitivity was due both to effects at the insulin receptor and direct effects on glycolysis, presumptively at phosphofructokinase. Reversal of these changes with bicarbonate was associated with a fall in hepatic ATP content. It is suggested that the insulin resistance of severe diabetic ketoacidosis in the rat is secondary to inhibitory effects of hydrogen ion; the exact mechanism remains to be established.

98. Haematological, serological and pathological effects in chicks of one or more intravenous injections of Salmonella gallinarum endotoxin. I. M. Smith, S. T. Licence, and R. Hill. Res. Vet. Sci. 24: 154-160, 1978.

Abnormalities appeared a few hours after groups of 14-day-old chicks were injected intravenously with 15 mg/kg of endotoxin (LPS) from Salmonella gallinarum. Clinical illness without mortality was accompanied by significant ($p<0.05$) falls in body temperature, bursa weight, the main haematological parameters, serum iron (SI) and transferrin saturation (TS) and a significant increase in unsaturated iron-binding capacity. All responses, apart from bursa weight, SI values and total and differential white-cell counts, returned to normal within 24 to 48 hr. LPS given daily for 3 consecutive days did not cause changes in the main haematological parameters during the 48 hr period following the third injection. However body and bursa weight and heterophil counts were significantly depressed, whereas body temperature, SI and TS were affected biphasically, first being depressed and then raised above normal. Chicks injected with LPS daily for 6 consecutive days showed broadly similar responses but a persistent microcytosis was also present.

99. Glucose metabolism in intact man: the responsiveness of splanchnic and peripheral tissues to insulin. D. Rabinowitz and J. E. Liljenquist. Metabolism 27 (Suppl. 2): 1832-38, 1978.

Man controls his blood sugar concentration within rather narrow limits, despite wide latitude in the content and timing of means. Man does not eat constantly; rather, he alternates between periods of "feasting" and "fasting". Man stores excess carbon largely as triglyceride; our glucose stores as glycogen are rather limited--certainly less than 0.5 kg. During food-free intervals, the liver is virtually the only source of blood glucose. Hepatic glucose output is about 2-3 mg/kg/min or about 150-180 mg/min. About 80-100 mg/min is distributed to the brain; another 30 mg/min, or only 1/6 of glucose output, is distributed to muscle, although muscle constitutes 40% of body mass. There is relatively

small, but important, contribution to tissues that are dependent upon glycolysis (e.g., the red cell and the renal medulla) and to other tissues. The liver contains only enough glucose as glycogen to maintain the blood sugar for 12-18 hr. Gluconeogenesis (the synthesis of new glucose from amino acids and other precursors) provides an alternate source of glucose. Important substrates for gluconeogenesis are the "glycogenic" amino acids (for example, alanine), glycerol, pyruvate, and lactate, all flowing to the liver from the periphery. In the post-absorptive state, 12 hr after food, this process may account for only 10% of hepatic glucose output, but with prolonged starvation, this fraction increases.

100. Insulin resistance, insulin insensitivity, and insulin unresponsiveness: a necessary distinction. C. R. Kahn. Metabolism 27 (Suppl. 2): 1893-1902, 1978.

Insulin resistance may be said to exist whenever normal concentrations of insulin produce a less than normal biologic response. Hormone resistant states may be divided into those due to decreased sensitivity to a hormone (i.e., a shift in the dose-response curve to the right), those due to a decrease in the maximal response to the hormone, and those that are combinations of decreased sensitivity and decreased responsiveness. This distinction is important, since the molecular mechanisms that produce these various forms of insulin resistance may be different. Disorders associated with alterations prior to the interaction of insulin with its receptor are more likely to produce states of decreased sensitivity, where disorders associated with alterations at the intracellular steps in insulin action are more likely to produce decreased responsiveness. With more precise use of these terms and a more complete understanding of insulin action, it will be possible to begin to segregate the roles of the various prereceptor, receptor and postreceptor factors that are involved in producing the differing patterns of metabolism observed in disease.

101. Platelet and fibrinogen production: relative sensitivities to endotoxin. B. M. Alving, B. L. Evatt, J. Levin, W. R. Bell, R. B. Ramsey, and F. C. Levin. J. Lab. Clin. Med. 93: 437-448, 1979.

The relative sensitivities of platelet and fibrinogen production to endotoxin were determined in male New Zealand rabbits. E. coli endotoxin was administered in single i.v. doses of 0.1 to 50.0 μ/g/kg body mass. ^{75}SeM was injected 5, 12, or 18 hr after endotoxin, and the percent incorporation into platelets and fibrinogen was used to measure thrombopoiesis and fibrinogen synthesis. Leukopenia occurred after the infusion of endotoxin at all dose levels; the lowest dose that caused thrombocytopenia was 0.5 μg/kg. Endotoxin was detected with the Limulus test in plasma of animals that received 5 to 50 μg/kg. The stimulation of fibrinogen and platelet production, as well as the postinfusion decrease in platelet count, correlated directly with the log of the dose of endotoxin infused. The lowest dose of endotoxin that stimulated platelet and fibrinogen production was 0.5 μg/kg. In animals that received this dose of endotoxin, increased fibrinogen production was detected only when ^{75}SeM was injected 5 hr later. In animals that received 50 μg/kg, increased fibrinogen production was observed when ^{75}SeM was injected 5, 12 or 18 hr later. Increased platelet production was detected at these two

doses only when ^{75}SeM was injected 18 hr after endotoxin. The data indicate that fibrinogen and platelet production have similar sensitivities to endotoxin, although the time course of stimulation is different for these two blood components.

102. Leucocytic changes in cows given intravenous injections of Escherichia coli endotoxin. N. C. Jain and J. Lasmanis. Res. Vet. Sci. 24: 386-7, 1978.

Single i.v. injections of Escherichia coli endotoxin into normal cows produced dose dependent leucocytic and febrile responses. Injections of 5 to 20 µg endotoxin induced a neutrophilia between 4 and 8 hr, whereas 50 to 500 µg produced a severe neutropenia for 4 to 6 hr followed by a gradual increase in neutrophils along with slight to moderate left shift. Higher doses caused progressively severe lymphopenia and greater increase in fever than the lower doses. It was concluded that blood leucocytic changes during the early part of endotoxin-induced mastitis are partly related to systemic absorption of endotoxin, and that the size of the bone marrow neutrophil reserve in the cow could be estimated by injecting 5 to 10 µg of endotoxin intravenously.

103. Survey for positive Limulus amoebocyte lysate test in plasma from humans and common research animals. D. DuBose, M. Lemaire, J. Brown, D. Wolfe, and M. Hamlet. J. Clin. Microbiol. 7: 139-141, 1978.

A survey for positive Limulus amoebocyte lysate tests was conducted on apparently healthy humans, mongrel dogs, rats, mice, rabbits, and squirrel monkeys. Only mongrel dog (45.8%) and human (32.8%) plasma samples gave positive tests. In dogs, a significant correlation between positive Limulus amoebocyte lysate tests and the presence of intestinal parasites was found. Positives found in human plasma samples were thought to be due to the presence of background levels of endotoxin or some possible mimicker substance found in the plasma after chloroform extraction. It was concluded that there was a need to distinguish between these positive Limulus tests and those which represent significant endotoxemia.

104. The modification of biophysical and endotoxic properties of bacterial lipopolysaccharides by serum. R. J. Ulevitch and A. R. Johnston. J. Clin. Invest. 62: 1313-1324, 1978.

Normal rabbit serum reduces the buoyant density of lipopolysaccharide (LPS) from Escherichia coli 0111:B4 and Salmonealla minnesota R595 to a value <1.2 g/cm^3. This density shift is associated with the inhibition of a number of endotoxic activities of the LPS; namely, the pyrogenic activity, the ability to produce an immediate neutropenia in rabbits, lethality in adrenalectomized mice, and anticomplementary activity. A qualitatively similar change in buoyant density was observed to occur after i.v. injection of the LPS into rabbits. Preliminary evidence suggests that the density shift does not occur as a result of the degradation of the glycolipid backbone of the LPS. These data suggest that the interactions of LPS with plasma (or serum) components leading to reduction in buoyant density may account for a major pathway of LPS detoxification.

105. Protein and fat utilization in shock. A. M. Daniel, C. H. Pierce, H. M. Shizgal, and L. D. MacLean. Surgery 84: 588-594, 1978.

A previous study demonstrated that in the dog, shock, regardless of its etiology, resulted in increased oxidative utilization of substrates which form lactate and pyruvate as intermediary metabolites. The study implied a concomitant decrease in free fatty acid oxidation, as the oxidative pathway of the latter does not involve the lactate-pyruvate step. To test this hypothesis, free fatty acid metabolism was investigated by infusing carbon-14 labelled fatty acid in 12 normal dogs, in 9 animals in shock due to controlled cardiac tamponade, and in 6 animals with endotoxin shock. The shock state was characterized by a significant decrease both in arterial fatty acid concentration and in free fatty acid turnover. In addition, both the rate of free fatty acid oxidation and the percentage of the total CO_2 derived from free fatty acid oxidation were significantly diminished. In contrast, urea production rates were higher in shock, and the calculated maximum contribution of protein oxidation to total CO_2 production rose from 23% in the control animals to 50% in the test groups.

106. Release of granulocyte elastase in lethal canine endotoxin shock. A. O. Aasen and K. Ohlsson. Hoppe-Seyler's Z. Physiol. Chem. 359: 683-690, 1978.

The release of granulocyte elastase and its interaction with plasma protease inhibitors was studied in dogs receiving a slow infusion of a lethal dose of Escherichia coli endotoxin. During endotoxin infusion a marked decline in leucocyte counts was paralleled by a rapid increase in plasma granulocyte elastase concentrations. Maximal values were reached after 3 hr, when the infusion was ended. Crossed immunoelectrophoresis with antiserum against granulocyte elastase did not reveal the presence of elastase components with the electrophoretic mobility of free elastase, but elastase-α_1-antitrypsin complexes were detected. A gradually decreasing plasma concentration of α_2- macroglobulin was noted during the experiments. Crossed immunoelectrophoresis, however, did not reveal any electrophoretic heterogeneity. It is concluded that the release of granulocyte proteases might be of significance for several pathophysiological changes seen in endotoxin shock.

107. Increased survival with methylprednisolone treatment in canine endotoxin shock. G. L. White, L. T. Archer, B. K. Beller, and L. B. Hinshaw. J. Surg. Res. 25: 357-364, 1978.

The use of corticosteroids has been intensively studied for the treatment of endotoxin shock; however, there still remains much controversy over their use. This study was designed to determine the therapeutic value of treatment with methylprednisolone sodium succinate in the awake and anesthetized canine receiving LD_{100} of E. coli endotoxin by either intravenous slow infusion or bolus injection. Methylprednisolone (30 mg/kg) was administered initially at 15 min following the onset of endotoxin infusion and then at 90 min given a maintenance infusion of 15 mg/kg for 120 min. It was found that treatment with methylprednisolone significantly increased survival rate (83%) in dogs receiving LD_{100} E. coli endotoxin by slow infusion in either the awake or anesthetized state. Both the 5-hr infusion and bolus injection of endotoxin

produced a 100% mortality if steroid was not administered. Treatment with methylprednisolone did not alter the 100% mortality in the canine bolus-injected endotoxin shock model. Survival was associated with a normoglycemia and stabilized hematocrit, while death was accompanied by hypoglycemia and severe hemoconcentration.

108. Leukocyte response and hypoglycemia in superlethal endotoxic shock. G. L. White, L. T. Archer, B. K. Beller, D. D. Holmes, and L. B. Hinshaw. Circ. Shock 4: 231-239, 1977.

This laboratory has documented a progressively developing hypoglycemia associated with systemic hypotension, hepatosplanchnic pathology, and death in endotoxin-shocked dogs. Recent data documented accelerated uptake of glucose in blood following endotoxin, with certain components of the buffy coat responsible for the increased uptake. The present study utilizing the awake dog assayed a possible protective role of leukocytes against the lethal effects of endotoxin. Animals were divided into paired groups: saline controls (Group I) and endotoxin experimentals (Group II). Group II animals were injected intravenously with sublethal doses of E. coli endotoxin on 2 successive days (Days 1 and 2), LD_{100} on the third day, and $2XLD_{100}$ on Day 4. The control group received equal volumes of saline on Days 1, 2 and 3, but on Day 4 received a superlethal dose of endotoxin identical to the experimental group. The awake dog became febrile and exhibited initial leukopenia with subsequent marked leukocytosis in response to endotoxin. Lethal hypoglycemia was not seen in animals demonstrating initial leukocytosis (zero time) on the day of superlethal endotoxin challenge, while animals with initial normal leukocyte counts died with low glucose concentrations (mean, 40 mg%). Results suggest that an initial leukocytosis and sustained gluconeogenic function are important factors in survivability to endotoxin shock.

109. In vitro effects of methylprednisolone sodium succinate and E. coli organisms on neutrophils in baboon blood. L. B. Hinshaw, B. K. Beller, J. A. Majde, L. T. Archer, and G. L. White. Circ. Shock 5: 271-278, 1978.

The corticosteroid methylprednisolone sodium succinate (MP) has been observed to prevent hypoglycemia in experimental septic shock; however, detrimental actions of various corticosteroids on polymorphonuclear leukocyte function have been reported. The present study was designed to determine if MP depresses glucose metabolism of leukocytes or adversely affects neutrophil survival, or whether it modifies the mortality rate of live E. coli in baboon blood in vitro. Results show that therapeutically effective concentrations (13 μg/ml blood) and high doses (130 μg/ml blood) of MP exert no detrimental influences on glucose utilization or survival of neutrophils in the absence or presence of E. coli organisms in concentrations of 4.2×10^7 and 2.3×10^8 organisms per milliliter blood. However, E. coli organisms increase neutrophil mortality rate and glucose uptake of the blood. These findings support the view that MP does not adversely influence leukocyte metabolism and survival, nor does it modify the mortality rate of live E. coli.

110. A pathologic study of Escherichia coli shock in the baboon and the response to adrenocorticosteroid treatment. J. J. Coalson, B. A. Benjamin, L. T. Archer, B. K. Beller, R. H. Spaet, and L. B. Hinshaw. Surg. Gynecol. Obstet. 147: 726-736, 1978.

This study was undertaken to determine if corticosteroids would prevent the development of the pathologic lesions of septic shock in baboons treated with live Escherichia coli organisms during a 24-hr study period. Pathologic changes were defined for multiple organs and compared with the lesions previously described in the shock state in humans. Eleven awake baboons were infused with comparable dosages of live E. coli organisms during a 5-hr period with one member of each pair receiving methylprednisolone. One additional baboon received saline solution in place of organisms and served as the control study. Autopsies were performed immediately, and specimens were obtained from the heart, lungs, liver, adrenals, kidneys, pancreas and gastrointestinal tract for light microscopic and ultrastructural studies.

Results of this study would indicate that adrenal corticosteroids do not prevent or decrease, or both, the severity of any of the morphologic lesions in the baboon subjected to low or high dosages of E. coli organisms. The pathologic changes induced by live E. coli organisms in the baboon include fibrin thrombi, edema or hemorrhage, or both, and necrosis of multiple organ systems. The liver, adrenal glands and kidneys show striking pathologic changes, whereas the gastrointestinal tract shows no significant pathologic alteration. Results of this morphologic study demonstrate that the shock lesions of the subhuman primate and human are remarkably similar.

111. Escherichia coli shock in the baboon and the response to adrenocorticosteroid treatment. L. B. Hinshaw, J. J. Coalson, B. A. Benjamin, L. T. Archer, B. K. Beller, O. R. Kling, E. M. Hasser, and R. W. Phillips. Surg. Gynecol. Obstet. 147: 545-557, 1978.

Results of recent studies from this laboratory have demonstrated that methylprednisolone sodium succinate increases the survival rate of dogs given LD_{100} Escherichia coli endotoxin. This study was undertaken to determine the effects of methylprednisolone on the baboon infused with live E. coli organisms. Awake baboons were paired by infusing intravenously comparable doses of E. coli during a 5-hr period. Baboons given methylprednisolone received bolus injections of 30 mg/kg at 15 min after beginning the infusion of E. coli and 2-hr infusions of 15 mg/kg at 2-hr intervals until death or for a 24-hr period. The mortality was unaltered by methylprednisolone. Six of seven baboons that were dying became progressively hypoglycemic, while hypoinsulinemia occurred in all baboons within 6 hr and was sustained until death. Systemic hypotension was observed, although pressures were variable. Potassium and lactate concentrations increased, while pH remained relatively constant in most baboons. Serum glutamic-pyruvic transaminase and arginase concentrations rose in most baboons dying within 18 hr. Results of morphologic studies revealed the presence of fibrin thrombi in the liver, kidney and adrenal tissue in most baboons. No significant differences in physiologic, metabolic, hematologic or morphologic parameters were observed between treated and untreated baboons.

112. Preserved liver function and leukocyte response in superlethal endotoxic shock. L. T. Archer, G. L. White, J. J. Coalson, B. K. Beller, O. Elmore, and L. B. Hinshaw. Circ. Shock 5: 279-289, 1978.

Recent studies reveal that endotoxin-pretreated awake dogs become markedly leukocytotic and survive superlethal endotoxin challenge without hypoglycemia. The purpose of this study was to determine if an association exists between leukocytosis, liver function, and survival in endotoxin shock. Studies were conducted on awake, conditioned adult dogs, with the experimental group (N=5) injected intravenously with 1/1000 LD_{100} E. coli endotoxin on Days 1 and 2, LD_{100} on Day 3, and $2xLD_{100}$ on Day 4. A control group (N=6) received equal volumes of saline on Days 1, 2 and 3, but on Day 4 received $2xLD_{100}$ endotoxin. All saline-pretreated dogs died within 7 hr following superlethal endotoxin challenge. Each animal in the experimental group was sacrificed at the time of its paired saline control's death for a comparison of liver pathology, since in parallel studies all endotoxin-pretreated dogs (N=11) survived for 30 days. Animals in the experimental group exhibited a marked leukocytosis of 30,000/cu mm on Day 4 compared with saline-pretreated controls. At the time of death the liver enzymes, arginase, and SGPT were significantly elevated in the saline-pretreated controls compared with the endotoxin-pretreated dogs. Liver pathology in endotoxin-pretreated dogs consisted of mild necrosis, while saline-pretreated animals demonstrated massive hepatocellular necrosis. Results support the view that increased numbers of neutrophils protect liver function and enhance survival in endotoxin shock.

113. Reversal of myocardial dysfunction in endotoxin shock with insulin. L. T. Archer, B. K. Beller, J. K. Drake, T. L. Whitsett, and L. B. Hinshaw. Canad. J. Physiol. Pharmacol. 56: 132-138, 1978.

Recent data reported from this laboratory have documented myocardial functional depression in endotoxin shock. The purpose of the present study was to determine the effects of insulin on the dysfunctioning canine myocardium subjected to lethal endotoxin shock. Experiments were conducted on isolated working left ventricular preparations in which LD_{60-100} endotoxin was administered prior to, or following, isolation of the heart. Determinations of myocardial performance were conducted under the conditions of controlled mean aortic pressure and cardiac output. Myocardial dysfunction occurred between 2 and 6 hr postendotoxin, as evidenced by significantly increased left ventricular end-diastolic pressure, decreased power, and depressed negative dP/dt, although blood glucose concentrations were maintained at control values. Intra-atrial infusions of insulin at rates of 6 U/min reversed all signs of myocardial dysfunction. During insulin infusion, heart rates decreased and myocardial lactate uptake increased while oxygen uptake and coronary blood flow were insignificantly altered.

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INDEXING TERMS

The University of Oklahoma at Oklahoma City
Health Sciences Center This publication was printed at no cost to the taxpayers of the State of Oklahoma.