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Abstract Reference List

Reviews of Pertinent Literature in Shock

L. B. Hinshaw

University of Oklahoma Health Sciences Center
Department of Physiology & Biophysics
Oklahoma City, Oklahoma

8 April 1977

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Reviews of Pertinent Literature in Shock •

(10) L. B. Hinshaw

University of Oklahoma Health Sciences Center
Department of Physiology & Biophysics
Oklahoma City, Oklahoma

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1. Adrenergic responses of the coronary vessels. G. Ross. Circ. Res. 39: 461-465, 1976.

The effects of stimulation of the cardiac sympathetic nerves and of circulating catecholamines on the heart and coronary circulation have been studied extensively for more than 80 years. The biochemical, electrophysiological, and mechanical responses of the myocardium have been described in considerable detail but surprisingly little is known about the adrenergic responses of the coronary vessels. This is because of the difficulty in separating the direct actions of adrenergic agents on coronary smooth muscle in the intact animal from the secondary effects induced by the almost simultaneous changes in transmural pressure and myocardial metabolism. A common approach to the problem of separating these effects has been to use adrenergic agents which selectively stimulate or block specific myocardial or coronary adrenotropic receptors.

The range of sympathetic neural control of the coronary vasculature appears to be small. There is evidence that sympathetic activity produces tonic coronary vasoconstriction in conscious dogs but inhibition of this tone by baroreceptor nerve stimulation or by lung inflation reduces coronary vascular resistance only 20-50%. Insufficient evidence exists to assess the direct effect of sympathetic nerve stimulation on coronary smooth muscle in conscious dogs because the only reported study was not designed to separate the direct and indirect effects. However, intravenous NE infusions at rates within the physiological range increase coronary vascular resistance by 13-14%. The significance of the vasoconstrictor tone and the adrenergic constriction which develops during NE administration is obscure. Both would oppose the metabolic dilator influences on the coronary arterioles and cause lower flow and a decreased myocardial PO2. It is difficult to imagine any beneficial consequences of these effects.

The physiological role of the coronary β-adrenotropic receptors is even less clear. It never has been unequivocally shown that sympathetic nerve stimulation can produce direct relaxation of coronary smooth muscle.

It is clear that more work needs to be done to establish the role of the adrenergic responses of coronary smooth muscle, particularly in conscious animals. No doubt improved methods of determining total and regional blood flow and myocardial oxygen consumption, together with use of more selective adrenergic blocking agents, will resolve some of the questions. Hopefully, the development of noninvasive methods may eventually enable the adrenergic response of the human coronary circulation to be assessed. These studies will have more than theoretical interest, since adrenergic activity has important implications in many facets of coronary disease, including coronary arterial spasm, collateral blood flow, infarct size, and cardiogenic shock.

2. Burn shock in untreated and saline-resuscitated guinea pigs. Development of a model. R. R. Wolfe and H. I. Miller. J. Surg. Res. 21: 269-276, 1976.

We developed a model for the study of burn shock in untreated and saline-resuscitated guinea pigs. The animals were anesthetized while being burned,

but were conscious and unrestrained throughout the experiment. The most dramatic postburn response in the untreated animals was an immediate and sustained reduction in cardiac output (CO). Saline resuscitation restored CO to its preburn level in 4 hr and improved 24-hr survival from 30 to 100%. When CO was restored in this manner, many of the alterations in physiological function in the burned, untreated animals returned to the level seen in the control group. The reductions in heart rate, oxygen consumption, core temperature, and pH, and the elevation in lactate evident in the burned, untreated animals were all back to the preburn levels in the resuscitated animals by 4 hr. These reversals suggested that the responses were secondary to a low CO. Hyperglycemia, on the other hand, persisted in the burned animals, regardless of whether or not saline resuscitation was begun. The control animals maintained stable values over time in all measures.

3. Granulocyte transfusions in leukopenic dogs: In vivo and in vitro function of granulocytes obtained by continuous-flow filtration leukopheresis. K. M. Debelak, R. B. Epstein, and B. R. Andersen. Blood 43: 757-766, 1974.

   The present studies were carried out to (1) evaluate a leukoadhesive technique for obtaining granulocytes for transfusion, (2) assess the granulocytes by in vitro techniques, and (3) determine the efficacy of granulocyte transfusion in preventing sepsis in leukopenic dogs. Dogs were rendered transiently leukopenic (<500 per cu mm) by intravenous cyclophosphamide, 40 mg/kg. Quantitative and qualitative blood cultures were obtained from all animals until death or hematologic recovery. Granulocytes were obtained on nylon filters by a continuous flow system and eluted with an ACD plasma saline solution. Granulocyte function was studied in vitro by chemotaxis, phagocytosis, intracellular filling, and electron microscopy. In vivo studies consisted of the measurement of granulocyte increments in transfused leukopenic dogs, T 1/2 of infused granulocytes, and protection of transfused dogs from septicemic episodes. Eluted granulocytes, when compared to normal controls, showed reduction in in vitro functions. These functions improved in granulocytes isolated posttransfusion from recipient dogs. An average of $3X10^{10}$ granulocytes could be obtained during a 1-hr leukopheresis of normal donors. Increments in recipient dogs averaged 2590 per cu mm. Five nontransfused leukopenic dogs developed septicemia and died within 7 days. Six dogs were treated with infusions of granulocytes. Three recovered completely, and three died of thrombocytopenic hemorrhage with negative blood cultures. One dog showed a transiently positive blood culture that became negative following transfusion. Septic episodes were significantly reduced in granulocyte transfused dogs ($p<0.01$). It was concluded that continuous-flow leukofiltration yielded granulocytes in sufficient number and with adequate functional capabilities to provide significant protection against septic death in the leukopenic host.

4. Glucocorticoid protection of the myocardial cell membrane and the reduction of edema in experimental acute myocardial ischemia. M. Feola, M. Rovetto, R. Soriano, S. Y. Cho, and L. Wiener. J. Thor. Cardiovasc. Surg. 72: 631-643, 1976.

   A possible protective effect of glucocorticoids on the ischemic myocardium was investigated in in situ dog hearts subjected to regional ischemia and in isolated rat hearts subjected to global ischemia. In the whole-animal preparation, the left anterior descending coronary artery (LAD) was occluded for 3 hours, or for 2 1/2 hours followed by 30 minutes of reperfusion. Dexamethasone phosphate was randomly administered (20 mg/kg i.v.) after

15 minutes of ischemia. Its effects were studied on the following: (1) myocardial cell membrane integrity, using electron microscopic examination of tissue biopsies treated with colloidal lanthanum; (2) myocardial water content, measuring the wet/dry weight of myocardial tissue; (3) ischemic injury, by a count of fuchsinophilic cells at light microscopy. In isolated rat hearts, ischemia was produced by a 60% reduction of coronary flow. Randomized hearts were perfused for 2 hours with dexamethasone, 15 mg/ml in buffered salt solution. Study included determination of tissue water content and coronary vascular resistance. Lanthanum was confined to the extracellular spaces in normal dog myocardium, but it was found all intracellularly after 3 hours of ischemia or after reperfusion. This was associated with morphologic changes characteristic of irreversible cell injury. In the hearts treated with dexamethasone, lanthanum remained excluded from the cells, water content was less ($p<0.005$), and fuchsinophilia less severe ($p<0.005$). Likewise, water content was less ($p<0.005$) and the increase in coronary vascular resistance resulting from ischemia less severe ($p<0.005$) in the dexamethasone-treated isolated rat hearts. Thus dexamethasone administered in pharmacologic doses, early, appeared to stabilize the cell membrane, limit myocardial edema, and reduce the severity of injury, both during ischemia and upon reperfusion.

5. The steroid effect on the in vitro human neutrophil chemotactic response. J. A. Majeski and J. W. Alexander. J. Surg. Res. 21: 265-268, 1976.

Clinical studies of neutrophils have led to the finding of a decreased neutrophil chemotactic response in various diseases. The lazy-leukocyte syndrome is now a well-known entity. Patients with severe overwhelming infections have depressed chemotaxis whereas patients with acute self-limiting infections have increased leukocyte chemotaxis.

Chemotaxis of the polymorphonuclear neutrophilic leukocyte was examined in vitro in the presence of the following steroids: medroxyprogesterone acetate, hydrocortisone sodium succinate, methylprednisolone sodium succinate, cortisone acetate, and prednisone acetate. Results indicate that high concentrations (1 mg/ml) of methylprednisolone sodium succinate inhibited the in vitro chemotactic response of human neutrophils. Results also indicate a mild inhibition of the neutrophil chemotactic response by hydrocortisone sodium succinate and prednisone acetate. Medroxyprogesterone acetate and cortisone acetate produced a mild stimulation of neutrophil chemotaxis. These results were discussed with emphasis on the quantitative differences found between in vivo and in vitro effect of steroids on the chemotactic response.

6. Effect of histamine and antihistamines on renal hemodynamics and functions in the isolated perfused canine kidney. W. B. Campbell and H. D. Itskovitz. J. Pharm. Exper. Ther. 198: 661-667, 1976.

Histamine was infused intra-arterially (10-40 µg/min) into isolated blood perfused canine kidneys while functional and hemodynamic parameters were monitored. When perfusion pressure (PP) was kept constant during the infusion of histamine, renal blood flow (RBF) increased from 137±9 to 181±9 ml/min ($p<.001$). A greater increase in RBF occurred to the inner renal cortex as measured by radioactive microspheres. The fractional outer/inner

cortical blood flow changed from 79:21 before histamine to 74:26 during its infusion ($p<.001$). Histamine did not alter creatinine clearance (C_{Cr}), urine volume (V), sodium excretion ($U_{Na}V$) or the fractional excretion of sodium (FE_{Na}) or water (FE_{H2O}) under these conditions. When renal blood flow was held constant during the infusion of histamine, PP decreased from 126/106±2 to 100/81±2 mmHg ($p<0.001$). This resulted in a reduction of absolute outer cortical (outer/inner) changed from 77:23 before histamine to 72:28 during its infusion ($p<.001$). In contrast to the effects of histamine at constant PP, C_{Cr}, V, $U_{Na}V$, FE_{Na}, and FE_{H2O} were decreased when histamine infusion reduced the PP. Administration of the H_1 receptor antagonist, diphenhydramine, blocked the hemodynamic effects of histamine whereas the administration of an H_2 receptor antagonist, metiamide, did not alter the histamine response. Similar vasodilatory responses to histamine were observed in isolated blood perfused dog and cat kidneys. In contrast, vasoconstrictor responses to histamine occurred in isolated dog and cat kidneys perfused with Krebs' solution and in isolated rabbit kidneys whether perfused with blood or Krebs' solution.

7. Measurement of glucose turnover in the human newborn with glucose-1-^{13}C. S. C. Kalhan, S. M. Savin, and P. A. J. Adam. J. Clin. Endocrin. Metab. 43: 704-707, 1976.

In order to meet his metabolic needs the newborn infant, after birth, must establish his own supply of glucose from either hepatic glycogen or gluconeogenesis. In the human newborn the rate of glucose production from these sources has not been quantified because of the potential risk of radiation associated with the use of radioactive tracers. Systemic glucose production rates were measured in 6 normal newborn infants by dilution of glucose-1-^{13}C tracer according to the prime constant-rate infusion technique. Glucose production rates were 4.4±0.39 mg/kg/min (mean±SD) in 4 infants at 2 hours of age, and were 3.83 and 3.86 mg/kg/min in 2 infants at 1 day of age. Systemic glucose production accounts for 50% of the substrate utilized for oxidative metabolism in newborn infants.

8. Frank-Starling relationship as an important determinant of fetal cardiac output. S. E. Kirkpatrick, P. T. Pitlick, J. Naliboff and W. F. Friedman. Am. J. Physiol. 231: 495-500, 1976.

The importance of the Frank-Starling mechanism was evaluated in 7 chronically instrumented fetal lambs (128-141 days gestation). Continuous determinations of left ventricular (LV) internal dimensions and pressures were obtained while LV end-diastolic diameter (LVEDD) was reduced by superior vena cava occlusion and increased by infusion of fetal blood into left atrium. A highly significant relationship was found to exist between stroke volume and LV extent of shortening (ΔD) ($r=+0.99$, $p<0.001$). Altering LVEDD from 10.5 to 13 mm or LV end diastolic pressure from 2.5 to 8 mmHg resulted in a 68% augmentation in ΔD. Spontaneous respiratory efforts resulted in frequent beat-to-beat variations in LVEDD and ΔD, which maintained cardiac output constant over a wide range of respiratory rates. Moreover, LV output determined by indicator-dilution techniques remained unchanged over a wide range of spontaneous heart rates (114-180 beats/min) as a result of changes in ΔD appropriate to alterations in LVEDD. Thus, changes in resting myocardial fiber length are of fundamental importance in fetal cardiovascular homeostasis and, within physiologic limits, it is quite clear that the Frank-Starling mechanism is operative and effective in the fetal lamb.

9. Interorgan transport of amino acids in hemorrhagic shock. D. H. Elwyn, H. C. Parikh, L. J. Stahr, S. I. Kim, and W. C. Shoemaker. Am. J. Physiol. 231: 377-386, 1976.

Arterial concentrations and net organ metabolism of amino acids (AA), O_2, CO_2, H^+, and glucose (Glc) were measured in two dogs before and during hemorrhage and after blood replacement. Shock caused increased splanchnic and decreased peripheral blood flow and O_2 consumption. PO_2 decreased more in hepatic venous than in mixed venous blood. pH fell in hemorrhage and increased with retransfusion. Increased liver output and arterial concentration of Glc were observed during hemorrhage. Differences between animals correlated with nutritional status. Blood concentrations of most AA showed little change during hemorrhage but increased after retransfusion. In contrast, arginine concentrations declined sharply. Peripheral output and hepatic uptake of most AA occurred during the control period. During shock, peripheral output and hepatic uptake of total AA and most individual AA declined progressively; after retransfusion peripheral uptake and hepatic output of many AA occurred. By contrast, peripheral output and hepatic uptake increased for alanine, glutamine, serine, phenylalanine, and tyrosine. After retransfusion net transport of some compounds occurred from periphery to liver; others, from liver to peripheraly. During shock, hepatic protein catabolism increased and this catabolism, accompanied by decreased hepatic uptake (increased hepatic output), seemed the main cause of increased blood AA concentrations. Protein catabolism in peripheral tissue was not a cause of increased blood concentrations. Pathological changes in pH, PO_2, and blood flow, occurred early in hemorrhage. In contrast, changes in AA movements and concentrations were within normal limits until late in shock.

10. Effect of angiotensin II antagonist infusion on autoregulation of renal blood flow. Y. Abe, T. Kishimoto, and K. Yamamoto. Am. J. Physiol. 231: 1267-1271, 1976.

The role of the renin-angiotensin system in the autoregulation of renal blood flow was examined in the anesthetized dog. The angiotensin II antagonist, [1-sarcosine, 8-isoleucine]angiotensin II, was continuously infused into the renal artery at rates of 1 and 3 μg/min, and renin secretion rate and intrarenal distribution of blood flow as well as total renal blood flow were measured during acute reductions in renal perfusion pressure within and below the range of autoregulation. Renal autoregulation and redistribution of blood flow by pressure reduction were not disturbed by the angiotensin II antagonist. This result does not provide any evidence for a primary role of the renin-angiotensin system in renal autoregulation. Redistribution of blood flow by pressure reduction occurred independently of the renin-angiotension system. It might depend on the differences in the resting tone among the zones.

11. Sources of error in glucose determinations in neonatal blood by glucose oxidase methods, including Dextrostix. R. E. Fox and D. Redstone. Am. J. Clin. Path. 66: 658-666, 1976.

An investigation was carried out to examine why a glucose oxidase-peroxidase-orthodianisidine method for plasma glucose, without protein precipitation, gave low results for neonatal blood. The magnitude of the difference between the results with and without protein precipitation was examined in a

clinical neonatal series, and in sera to which bilirubin, hemolysate, pure hemoglobin, and uric acid had been added. Systematic linear inhibition was demonstrated with bilirubin, and the results suggested that high concentrations of hemolysate and uric acid could also interfere. Use of alkaline protein precipitants eliminated the inhibition. Dextrostix test results for neonatal blood are compared with results of conventional glucose analyses and possible sources of discrepancy examined.

12. A filtration model for study of leukocyte transit in the microcirculation. L. M. K. Tanner and R. B. Scott. Am. J. Hematol. 1: 293-305, 1976.

In order to study characteristics of leukocytes which would be important determinants of their flow in the microcirculation, a model system was tested which utilizes in vitro filtration of leukocytes. Normal human peripheral blood leukocytes (85-90% granulocytes) were studied with filters with uniform 8 µm pore size.

Studies were performed to determine the effects of EDTA, temperature, hydrostatic pressure, pH, and osmolarity on filtration. Filterability was optimal at 0.2% EDTA, 10 cm hydrostatic pressure, neutral pH, isotonicity, and at room temperature.

Filtration was slowed greatly at leukocyte concentrations exceeding $25X10^9$ / liter. When leukocyte membranes were altered by formalin fixation, filtration slowed greatly, indicating that deformability is an important determinant of flow through small orifices. When mixtures of erythrocytes and leukocytes were filtered, there was a paradoxically enhanced transit of leukocytes compared to filtration of leukocytes alone, indicating interactions between these cells which alter flow.

These studies serve to characterize this model system which can be used to study the contribution to flow in the microcirculation of both normal and pathological leukocytes.

13. Die wirkung von dopamin im hamorrhagischen schock auf die durchblutung des pankreas. (The effect of dopamin on the microcirculation on the pancreas in hemorrhagic shock.) A. Ciesielski, P. Nagel, K. Lanser, and Y. Sill. Res. Exp. Med. 168: 35-44, 1976.

The influence of dopamine on microcirculation during hemorrhagic shock was investigated by means of the pancreas chamber technique (HEISIG, 1967). Parameter of microcirculation was the corpuscular flow velocity measured with the "Flying spot" method. Simultaneously arterial and venous blood pressure, heart rate, blood gases and pH-status were registered.

While a dopamine-dosage of 5 µg/kg/min did not markedly effect perfusion of the pancreas, application of 10 as well as 20 µg/kg/min dopamine caused a significant improvement of microcirculation. There was no difference between 10 and 20 µg/kg/min dopamine. The increase of capillary perfusion can certainly not be explained by the small rise of blood pressure that was found under treatment with dopamine. The results support the statement of the existence of dopamine-specific receptors in pancreatic vessels.

Compared to a group of animals treated with 5 µg/kg/min dopamine and an untreated control group, survival rates of animals treated with 10 as well as 20 µg/kg/min dopamine was significantly increased.

14. Kihlenhydrat- und fettstoffwechsel der skelettmuskulatur unter ruhebedingungen und bei kurzfristiger submaximaler arbeit am modell des perfundierten hinterbeins der ratte. (Muscle metabolism of glucose, lactate, free fatty acids, and glycerol at rest and during electrically stimulated exercise in the perfused rat hind limb.) C. Dieterle, R. Gärtner, and P. Dieterle. Res. Exp. Med. 168: 23-33, 1976.

The influence of insulin on muscle metabolism at rest and during electrically stimulated exercise was examined in the perfused rat hind limb. Basal glucose uptake of muscle tissue was enhanced threefold both by muscle contraction and by addition of physiological amounts of insulin. A further increase in glucose uptake was seen, when muscle was exercised in the presence of insulin. Lactate production rose 7-8fold by contractions. Insulin had no additional effect on lactate production during exercise. The work-induced lactate output exceeded glucose uptake, corresponding to a significantly reduced glycogen content after exercise. Basal lipolysis was not stimulated by muscle contractions. At rest the addition of both corticosterone and thyroxine did not increase the basal lipolysis. Yet, glycerol release rose twofold by the addition of serum to the perfusion medium. It is assumed that in the perfused rat hind limb glycogenolysis will promptly be stimulated by muscle contractions, whereas lipolysis cannot be enhanced by exercise alone.

15. Positive end-expiratory pressure (PEEP) ventilation. A review of mechanisms and actions. K. S. Wayne. J. Am. Med. Assn. 236: 1394-1396, 1976.

In situations characterized by a substantial decrease in lung compliance and a large alveolar-arterial oxygen tension gradient, positive end-expiratory pressure (PEEP) ventilation is often effective in enhancing arterial oxygen content. It may have a variable effect on cardiac output based in part on the level of end-expiratory pressure, the state of intravascular volume, and the pathophysiology of the underlying pulmonary abnormality. It is most beneficial in conditions manifesting diminished lung compliance. Evidence is clear that PEEP may decrease expiratory shunting by maintaining alveolar patency, thereby increasing functional residual capacity. It may not prevent and may actually favor accumulation of interstitial lung water. Commonly employed levels of PEEP result in a 7% incidence of pneumothorax. The most advantageous level of PEEP is variable and is determined by sequential monitoring of multiple physiologic indexes.

16. Percutaneous microsensing of muscle pH during shock and resuscitation. T. L. W. Kung, O. H. LeBlanc, Jr., and G. Moss. J. Surg. Res. 21: 285-289, 1976.

Muscle pH was monitored continuously during hypovolemic shock and during resuscitation in beagles, using a disposable, newly developed, flexible pH sensor that can be implanted percutaneously. The results demonstrate that muscle pH is superior to arterial or venous blood gases or pH as an index of peripheral tissue perfusion. The continuous nature of the pH monitoring is important, because it is the rate of change of peripheral muscle pH, rather than its absolute value, that is the measure of deterioration or improvement in perfusion status.

17. Granulocyte function in chronic granulocytic leukemia. II. Bactericidal capacity, phagocytic rate, oxygen consumption, and granule protein composition in isolated granulocytes. T. Olofsson, H. Odeberg, and I. Olsson. Blood 48: 581-593, 1976.

The initial rate of phagocytosis, oxygen consumption rate during phagocytosis, bactericidal capacity against Escherichia coli, and the granule protein composition of isolated mature-appearing granulocytes were studied in 23 patients with chronic granulocytic leukemia (CG) with the simultaneous use of normal controls. The initial rate of phagocytosis was decreased ($p<0.05$) in the CGL patient group, as were oxygen consumption rate ($p<0.001$) and bactericidal capacity ($p<0.001$). Kinetic analysis of the ingestion rate showed CGL granulocytes to have the same capacity to bind the particles as normal granulocytes. Both specific and primary granule protein deficiencies were shown for CGL granulocytes, and these deficiencies were more pronounced at or near blast cell transformation. Analysis of all different granulocyte function parameters showed an inverse correlation to white blood cell counts ($p<0.01$) and to the percentage of immature granulocytes in peripheral blood ($p<0.001$). The leukocytosis doubling time was progressively shortened during the chronic course of the disease. A correlation was found between granulocyte function parameters and leukocytosis doubling time ($p<0.001$), indicating that granulocyte function was progressively deteriorating during chronic phase CGL, and may be an expression of increasing disturbance of the differentiation process.

18. The effect of leukocyte and platelet transfusion on the activation of intravascular coagulation by endotoxin in granulocytopenic and thrombocytopenic rabbits. E. Bohn and G. Muller-Berghaus. Am. J. Path. 84: 239-258, 1976.

The effect of transfusion of peritoneal leukocytes, platelets, or cell suspension medium on the activation of intravascular coagulation and on the generation of capillary microclots was studied in 51 granulocytopenic and thrombocytopenic rabbits. Granulocytopenia and thrombocytopenia induced by feeding the cytotoxic drug busulfan prevented the activation of intravascular coagulation and the occurrence of renal glomerular microclots after two injections of endotoxin. The transfusion of platelets into busulfan-pretreated rabbits increased the mean platelet count from 2,400 to 205,000 cells/µl, but platelet-transfused rabbits did not exhibit activation of intravascular coagulation after endotoxin injection. If, however, granulocytopenic and thrombocytopenic rabbits were transfused with peritoneal leukocytes (1.0×10^9 cells/kg) before the second injection of endotoxin, activation of intravascular coagulation occurred, and microclot formation in renal glomerular capillaries was observed in a high percentage of animals. Positive reactions to endotoxin were obtained in leukocyte-transfused rabbits even with platelet counts of 1,000 cells/µl before the second injection of endotoxin. Thus platelets do not seem to be essentially involved in the activation of intravascular coagulation by endotoxin, whereas the presence of leukocytes is required for triggering endotoxin-induced generalized intravascular coagulation.

19. The renal response to acute injury and sepsis. C. E. Lucas. Surg. Clin. N. Am. 56: 953-975, 1976.

When a patient receives an overwhelming insult such as hypovolemic shock, the kidney responds by maintaining plasma volume at the expense of its own perfusion. Fortunately, the kidney's recuperative powers are excellent; most such transient stresses are readily overcome with a rapid return of normal renal function. The kidney has special interest to surgeons since renal function is affected by general anesthesia, intraoperative manipulation, general stress, hemorrhage, hypovolemia from trauma, postoperative fluid shifts, and sepsis. This interest led to the creation of a Surgical Renal Study Unit. Most of the concepts and quantitative data presented herein

reflect both the results of these studies and the clinical response to therapy. These clinical and functional studies have also determined distinct differences between the renal and systemic response to trauma with hypovolemia and severe sepsis.

The renal response to sepsis is, for the most part, a renal adaptation to an altered systemic circulatory status. Those factors which have created the most controversy regarding this response, therefore, are an extension of the controversy regarding the cardiovascular response to sepsis. Historically, sepsis has been characterized as a hypodynamic state with increased total peripheral resistance (TPR) and decreased cardiac output (CO); the kidneys, traditionally, shared in this response with increased RVR and decreased RBF, especially, outer cortical flow. These traditional concepts, however, reflect endotoxin studies in animals and a poor understanding of fluid shifts in man.

The empirical recognition that septic patients respond better to a fluid challenge and the clinical investigation of this response showed an expanded plasma volume, increased cardiac output, decreased TPR, increased ECF, and increased urine volume. This hemodynamic response has been called a "hyperdynamic state". Polyuria is present in most severely septic patients if resuscitation was initiated early enough to prevent renal ischemia and shutdown. Furthermore, polyuria may be inappropriate and persist despite later fluid restriction leading to subsequent hypovolemia.

20. The lung: Responses to trauma, surgery, and sepsis. E. F. Hirsch, J. R. Clarke, H. E. Gomez-Engler, and G. H. A. Clowes, Jr. Surg. Clin. N. Amer. 56: 909-928, 1976.

The adult pulmonary distress syndrome is a disease of many etiologies and significantly contributes to the post-traumatic and postsurgical mortality and morbidity. Pulmonary insufficiency associated with shock and hemorrhage is characterized by its relatively short duration, less severe alterations of pulmonary functions, and normal pulmonary vascular resistance. The judicious use of fluids and emphasis in the early use of blood during resuscitation will minimize the magnitude of the pulmonary insult.

Severe changes in oxygenation and ventilation, increases in pulmonary vascular resistance, the need for long-term respiratory assistance, and an increase in mortality and morbidity are characteristic of the adult pulmonary distress syndrome that follows severe systemic sepsis. Early aggressive pulmonary support is required in all life-threatenining surgical conditions. Endotracheal intubation is preferred to tracheostomy, and the use of a volume respirator will facilitate the control of ventilation and oxygenation.

Significant decreases in the functional residual capacity which are responsible for refractory hypoxemia and the use of high concentrations of oxygen can be circumvented by the use of positive end expiratory pressure. PEEP is sometimes associated with a decrease in cardiac output and an increase in the pulmonary shunt and occasionally pneumothorax. Continued hemodynamic and pulmonary monitoring of patients is mandatory when using PEEP.

Discontinuance of ventilatory assistance is usually possible if the pulmonary shunts are less than 25%, the tidal volumes greater than 5 cc/kg, and the vital capacity at least twice the tidal volume. Recovery from pulmonary

insufficiency is predicated on adequate pulmonary management, nutritional support, and the control of the underlying contributory conditions.

21. Colloid oncotic pressure and levels of albumin and total protein during major surgical procedures. W. S. Howland, O. Schweizer, J. Ragasa, and D. Jascott. Surg. Gynec. Obstet. 143: 592-596, 1976.

From the results of this study, it appears that whole blood alone or red blood cells reconstituted with saline solution do not adequately replace the loss of albumin and concomitant decrease in colloid oncotic pressure that occur during extensive intra-abdominal and intrathoracic operations. Since colloid oncotic pressure is a major factor in the restitution of intravascular volume from stores of interstitial fluid and since it may also play a role in the development of postoperative pulmonary problems, it is important to maintain a relatively normal colloid oncotic pressure during the operation and in the immediate postoperative period. Although dextran can be used for this purpose, its short half-life of 4-6 hr and associated coagulation problems militate against its use in large quantities. This leaves purified protein fraction or salt-poor albumin as the main sources of protein for the maintenance of colloid oncotic pressure. Both of these products are expensive and short in supply.

The oncometer in present use is a clinically feasible and rapid, 1-3 min, means of determining the colloid oncotic pressure. It permits a rational approach to the use of albumin products, avoiding the pitfalls of under or excess administration in the operative and postoperative periods.

22. Skeletal muscle metabolites as possible indicators of imminent death in acute hemorrhage. B. Amundson and H. Haljamäe. Eur. Surg. Res. 8: 311-320, 1976.

The extent to which changes in tissue energy metabolism correspond to the severity of a hemorrhagic shock condition has been studied. In cats, 50% of the blood volume was withdrawn within 10 min, resulting in a fatal outcome within 3 hr (range from 45 min to 3 hr). Skeletal muscle and blood samples were taken prior to the hemorrhage and in the agonal phase or after 2 hr in compensated bled animals. Tissue levels of ATP, CrP, G-6-P, lactate and glucose as well as blood levels of glucose, lactate and pyruvate were determined enzymatically. The results showed no depletion of phosphagen levels in the agonal phase, while glycolytic metabolites, lactate in particular, demonstrated a close correlation to circulatory deterioration and imminent death.

23. Interest of isoproterenol in the treatment of hemorrhagic shock in dogs. R. Rettmann and Ch. de Muylder. Eur. Surg. Res. 8: 321-336, 1976.

Four groups of experiments were focused on two problems: first, the replacement of the substracted amount of blood, and second, the correction of the peripheral reactions to substantial blood loss, namely vasoconstriction and acidosis. We stuck to a simple plan in our experiments: lost blood was entirely collected and retransfused. In 26 cases out of 37, we used isoproterenol hydrochloride (Isuprel, Winthrop) to open the peripheral vascular bed. In six different groups we followed the response to variations of retransfusion and administration of isoproterenol. Several parameters were studied: arterial blood pressure, central venous pressure, rectal temperature and pH. The association of blood transfusion with injection of isoproterenol, in adequate amounts to correct hypovolemia and to prevent vasoconstriction, is undoubtedly the best treatment of hemorrhagic shock.

24. Brain metabolism in the critically ill. B. K. Siesjö, C. Carlsson, M. Hägerdal, and C.-H. Nordström. Crit. Care Med. 4: 283-294, 1976.

A large number of clinical conditions are associated with a transient or permanent disturbance of brain function. Common to all of them is that, in some way, brain metabolism is changed from the normal. These changes cover a vast spectrum, ranging from the subtle alterations of metabolism encountered in mental disease to those underlying death and dissolution of cells in conditions of oxygen lack. This communication is concerned with brain metabolism in the critically ill with emphasis on conditions of hypoglycemia, hypoxia, and ischemia. We begin by briefly recalling the salient features of brain metabolism in the healthy individual. Since clinicians caring for critically ill patients take an interest in factors that may aggravate the primary disease and in measures that may prevent or minimize its final effect on the brain, we will also briefly consider how brain metabolism is influenced by potentially harmful factors (hyperthermia, anxiety and stress, and tissue acidosis due to CO_2 retention) as well as by measures that are often instituted to ameliorate the effects of hypoxia and ischemia (hypothermia, administration of anesthetics and sedatives).

25. Metabolic abnormalities of shock. A. E. Baue. Surg. Clin. N. Am. 56: 1059-1071, 1976.

Alterations in metabolism produced by decreased blood flow, circulatory failure, or shock may be considered from the standpoint of what happens to the individual as a whole, what happens in each organ system, and changes in the parenchymal cells of each organ. Metabolic changes of the entire organism will be reflected in changes in the constituents of the blood with varying contributions or deficiencies by the several organs. Metabolic changes in individual organs may be reflected in changes in functions of that organ and often can be measured in man. Abnormalities of metabolism of cells and subcellular organelles can presently only be studied in detail in experimental animals with occasional measurements in man where tissue can be sampled. The metabolic abnormalities of shock are secondary changes resulting from decreased blood flow, decreased oxygen and nutrient delivery to tissue, and decreased removal of waste products. These circulatory problems are modified or augmented by complex neuroendocrine activity, by sepsis, by altered nutrition, and by other changes. Thus, metabolic abnormalities are inextricably related to, produced by, or produce abnormalities such as acid-base balance, endocrine responses, energy metabolism, body water, and others. Finally, all changes produced by shock can be considered metabolic abnormalities since they result from changes in cell function and metabolism. This article is a description of metabolic changes with shock, their impact in the individual, and what might be done about them.

26. Fluid, electrolyte, and acid-base balance. H. T. Randall. Surg. Clin. N.Am. 56: 1019-1058, 1976.

This discussion considers body composition including body cell mass and supporting and protecting tissues; fluid compartments and their size, composition, and function; metabolism of water and electrolytes, and the regulatory mechanisms that defend the volume, content, and acid-base balance of the body. With these as background, alterations in water balance, in electrolyte composition and distribution, and acidosis and alkalosis are analyzed. Parenteral fluid and

electrolyte therapy are discussed as an alternative and often necessary means of maintaining or correcting abnormalities in fluid, electrolyte, and acid-base balances.

A thorough understanding of the physiologic principles underlying fluid, electrolyte, and acid-base balance and of the compensatory mechanisms that come into play when disease, trauma, sepsis, or surgery distort normal patterns is essential, if the surgeon is to recognize malfunction where he sees it, and take appropriate steps to correct it. Failure to do so substantially increases both morbidity and mortality in seriously ill patients.

27. Metabolic adaptations for energy production during trauma and sepsis. N. T. Ryan. Surg. Clin. N. Am. 56: 1073-1090, 1976.

Recovery from trauma with extensive bacterial infection requires a vigorous response by metabolically active cells and tissues. High cardiac output, maintenance of blood volume and hematocrit, increased metabolic rate with or without fever, synthesis of immune proteins, and the proliferation and antibacterial activity of immunocompetent cells, maintenance of adequate pulmonary ventilation, in addition to cellular and wound repair, all require provision of metabolic energy sources and necessary biosynthetic precursors. The biochemical adaptation evoked by the body to provide these necessary materials is unique to the post-traumatic or septic state, and differs in important respects from the physiologic responses to fasting, starvation, exercise, cold, or other conditions.

This review focuses on the major metabolic consequences of trauma and sepsis, examines the control mechanisms which are disrupted, and suggests possible biochemical explanations for certain components of the response. It is so arranged that first the general features of the response are described, and the consequences of them are discussed; subsequently the detailed mechanisms are presented with laboratory and clinical data and with relevant biochemical explanations.

28. Endocrine control of plasma protein and volume. D. S. Gann. Surg. Clin. N. Am. 56: 1135-1145, 1976.

The loss of blood volume initiates a sequence of events that begin with detection of the volume loss by cardiovascular receptors and the transmission of the signals of that loss to the central nervous system. Central neural processing leads to the release of multiple hormones that act together to induce an increase in extracellular osmolality. In response to the increase in extracellular osmolality, fluid shifts from cells to the interstitium, increasing interstitial volume and pressure. The increase in interstitial pressure leads to increased capillary and lymphatic return of fluid and to increased lymphatic return of preformed albumin. These events combine to form the second definitive phase of the restitution of blood volume, which is crucial both for the support of critical cardiovascular function and for the inhibition of the initial neuroendocrine response. If left unabated, this response may lead to the detrimental features of the metabolic response to injury. The degree of hyperosmolality following volume loss in injury may serve as an index of severity of that injury. The presence of the mechanism outlined provides a further rationale arguing in favor of prompt and adequate fluid therapy of the injured and volume-depleted patient.

29. Energy metabolism and proteolysis in traumatized and septic man. G. H. A. Clowes, Jr., T. F. O'Donnell, G. L. Blackburn, and T. N. Maki. Surg. Clin. N. Am. 56: 1169-1184, 1976.

Contrasting with normal starvation, the severe proteolysis and excessive gluconeogenesis typical of sepsis and trauma are in general proportional to the total injury inflicted upon tissues both locally and in distant organs throughout the body. Evidence from observations on the utilization of substrates by peripheral tissues strongly suggest the relationship of proteolysis and glucogenesis to the presence of an energy fuel deficit in skeletal muscle, whether established by an insulin resistance or by insufficient perfusion in shock.

In the presence of the high cardiac output, characteristic of the patient who will recover, muscle insulin resistance is indicated by the lack of increased glucose uptake by the leg despite hyperglycemia and elevated blood insulin. On the other hand, a reduction of blood free fatty acids suggests that adipose tissue continues to respond to insulin. To satisfy the resulting energy fuel deficit occasioned by increased lactate production and by reduced availability of both free fatty acid and ketones, branch chain amino acids (BAA) are oxidized in the muscles. Alanine is produced by transamination. Hepatic glucogenesis and ureagenesis are stimulated to clear from the blood the lactate, alanine, and other glucogenic precursors. In shock the metabolic defect is compounded by severly reduced insulin secretion and by tissue hypoxia.

Thus, the insulin resistance and energy fuel deficit in muscle makes available large quantities of glucose derived from muscle amino acids or lactate. From a long term point of view, the deficit in the amino acid pool thus created causes progressive failure of protein resynthesis or de novo synthesis in all organs. If unchecked, this defect may be fatal. Much can be done to support the patient by the correct use of alimentation whether by the gastrointestinal tract or parenterally. In the low output shock hypoinsulinemia state, some success in restoring normal cardiac function and metabolism generally has been attained by the administration of large doses of insulin.

Vital function of every cell, including enzyme activity, motion, and hundreds of others essential to survival, depend upon energy and synthesis. Not only are fuels required to satisfy this need but each organ is dependent upon the function of others to continue its own. Because of the far reaching detrimental effects of trauma and sepsis throughout the body, it is of the greatest importance to understand the physiologic responses including a high cardiac output, which characterize the pattern of survival and recovery. In addition, to correct alimentation treatment of failure in any system, circulatory, respiratory, renal, or other must be directed toward restoration of the physiologic pattern of recovery.

30. Nutritional care of the injured and/or septic patient. G. L. Blackburn and B. R. Bistrian. Surg. Clin. N. Am. 56: 1195-1224, 1976.

Trauma, sepsis, and injury have long been recognized as producing significant alterations in body metabolism. This response--initiated by the central nervous system--is sympathetically mediated and triggers the release of

substrate-mobilizing hormones. The stress of illness effects a glucocorticoid-induced catabolism of peripheral protein resulting in an overall negative nitrogen balance. Recently we have realized that this peripheral catabolism might provide amino acids for the synthesis of acutely needed blood proteins, structural proteins, and enzymes. This response is quite different from starvation without injury in which initial losses are from the liver and other labile visceral protein; it is only after 3 or 4 days of starvation that substantial mobilization of skeletal protein begins to take place.

The acute phase of illness gives way to an adaptive phase during which the organism seeks to adapt its metabolism to the changes in the nature and source of nutrition. The timing of the transition between phases is dependent upon the degree of illness, injury or sepsis, and associated nutritional depletion. Effective nutritional support can occur in this adaptive phase because the strong catabolic signals resulting from the high levels of catecholamines and glucocorticoids have subsided. The hormonal situation is complex, but the adaptive phase is recognized by the falling blood glucose, normal blood urea nitrogen, ketosis, ketonuria, and decreasing excretion of urea nitrogen. A fall in the blood glucose is of major significance in identifying this transition since it is well recognized that a high catabolic rate is associated with increased rates of gluconeogenesis and hyperglycemia. It should be stressed that the administration of exogenous glucose, such as the infusion of 5% dextrose solutions, prevents thd identification of this transition and furthermore does not conserve the body's protein during the acute phase of injury.

Thus one can see that a knowledge of the metabolic response to illness is necessary for the development of effective nutritional support plans; the phase of the response to injury, the extent of nutritional depletion, and the degree of hypercatabolism will influence the timing of therapy and patient benefits.

31. The effects of coronary vasodilatation on cardiac performance during endotoxin shock. M. D. Peyton, L. B. Hinshaw, L. J. Greenfield, and R. C. Elkins. Surg. Gynec. Obstet. 143: 533-538, 1976.

Results of studies have suggested that endotoxin and lowered coronary arterial perfusion pressures are detrimental to cardiac performance and lead to failure. Prevention of cardiac failure in the isolated canine heart preparation confronted with endotoxin and decreased coronary perfusion pressure was possible by perfusing these hearts with sodium nitroprusside. Prevention of failure was manifested by a lowered left ventricular end-diastolic pressure and was associated with increased coronary flow and decreased coronary resistance with increased oxygen delivery and decreased oxygen extraction. Possible explanations for improved performance by dilator perfusion include increased delivery of oxygen and nutrients to myocardial tissue as well as a reduction of ventricular wall tension by dilating the coronary vascular skeleton. Prevention of extravasation of interstitial fluid into myocardial tissue by reducing overperfusion of potentially damaged coronary vessels could serve to maintain myocardial integrity and ventricular compliance. The potential use of such therapy warrants further study, with emphasis on evaluating the hemodynamics of the intact animal.

32. Comparison of hemodynamic and regional blood flow changes at equivalent stages of endotoxin and hemorrhagic shock. R. B. Rutherford, J. V. Balis, R. S. Trow, and G. M. Graves. J. Trauma 16: 886-897, 1976.

Hemodynamic, respiratory and regional blood flow measurements were carried out in two groups of monkeys at three roughly equivalent stages of endotoxin and hemorrhagic shock. Comparisons revealed characteristic differences at the two early stages, particularly in systemic vascular resistance and the pattern of distribution of cardiac output. However, at the final stage of shock, these patterns had merged and there were no characteristic differences between the two groups. The pathologic significance of these findings, in terms of the endotoxin theory of irreversible hemorrhagic shock and the relative contributions of vasoactive humoral substances at various stages of the two forms of shock, is discussed.

33. Altered neutrophil phagocytic function in burn patients. J. B. Grogan. J. Trauma 16: 734-738, 1976.

The role of the peripheral blood phagocyte in host resistance to infection is receiving much attention at the present time. It is clear that an ineffective phagocytic system can contribute to serious septic complications in injured patients. Since infection remains a major hazard in burns, more information is needed to better understand the basic defects in the host defense system which contribute to the high incidence of infection in burns.

Neutrophil ingestion and bactericidal capacity were studied in 35 burn patients. Using Pseudomonas aeruginosa as the test microorganism, it was found that defects in bactericidal capacity were common, particularly in phagocytes of patients with burns greater than 30% of the body surface. Even though reduced neutrophil ingestion was observed in a significant number of assays the incidence was low in comparison to the incidence of reduced bactericidal capacity. Defects in phagocytic function were not detected until at least 5 days after injury and at the time of discharge all patients that were studied had resumed normal phagocytic function.

34. A modified leukocyte nitroblue tetrazolium test in acute bacterial infection. R. M. Miller, J. Garbus, A. R. Schwartz, H. L. DuPont, M. M. Levine, D. F. Clyde, and R. B. Hornick. Am. J. Clin. Path. 66: 905-910, 1976.

The increased ability of leukocytes to reduce nitroblue tetrazolium (NBT) has been used to detect the presence of systemic bacterial infection. This test has been utilized to evaluate infections and leukocyte dysfunction in children, but has not been extensively applied to traumatized patients or infected volunteers. Moreover, the technic as originally described presented methodologic difficulties. In this study of 889 such patients, a modified NBT test provided excellent differentiation of 63 systemic bacterial infections (NBT socre$\geq$10%) from non-infectious fevers, local enteric diseases, and certain viral and plasmodial infections (NBT score$\leq$9%). Splenectomy was associated with a transient fasle-positive socre and clinical typhoid fever with a false-negative response.

35. Evidence for a glucocorticoid receptor in human leukocytes. B. Simonsson. Acta Physiol. Scand. 98: 131-135, 1976.

The glucocorticoid uptake in vitro by human periferal leukocytes was studied. The uptake showed 2 main components, one saturable and one non-saturable. The saturable component was compared with the uptake by the specific glucocorticoid receptor in rabbit granulocytes. The similarities with the rabbit receptor in structural specificity, time course of uptake at 37°C, sensitivity to metabolic inhibition by PCMS and the physiological concentration for half saturation indicate that the saturable component corresponds to a specific glucocorticoid receptor. Cells from chronic lymphatic leukemia and chronic myeloic leukemia were also studied. Only the former had a saturable glucocorticoid uptake.

36. Localization of glucocorticoid uptake in normal and ischemic myocardial tissue of isolated perfused cat hearts. M. Okuda, K. R. Young, Jr., and A. M. Lefer. Circ. Res. 39: 640-646, 1976.

We studied the uptake of labeled dexamethasone (^{3}H-Dex) or methylprednisolone (^{3}H-MP) in isolated perfused cat hearts during the first hour of acute myocardial ischemia. Considerable amounts of ^{3}H-Dex and ^{3}H-MP were taken up by the plasma membrane (F_1) fraction in control, border zone, and ischemic myocardial tissue. Lesser amounts were incorporated into the remaining cell fractions. A gradient of glucocorticoid uptake was observed that decreased from control tissue to ischemic tissue in all subcellular fractions (i.e., F_1 to F_5). Accordingly, supernatant fraction (S) to particulate (P) ratios of labeled glucocorticoid uptake increased from control to ischemic tissue, indicating that myocardial cell damage resulted in a decrease in glucocorticoid-binding capacity in subcellular fractions obtained from ischemic tissue. The activity of 5'-nucleotidase (5'ND), a plasma membrane marker in myocardial cells, also decreased from normal to ischemic tissue. Furthermore, we found that uptake of ^{3}H-MP and ^{3}H-Dex was associated with the retention of 5'ND activity in F_1 fractions of both border zone and ischemic tissue. Similar protection of plasma membrane integrity occurred in the supernatant fraction as determined by changes in S/P ratios of 5'ND activity. These data provide support for the concepts that (1) plasma membrane changes occur soon after acute myocardial ischemia, and (2) the mechanism by which glucocorticoids exert a protective effect in myocardial ischemia may be related to membrane stabilization.

37. Insulin secretion and sensitization to endotoxin shock. B. J. Buchanan and J. P. Filkins. Circ. Shock 3: 223-230, 1976.

The relationship between insulinemia and sensitivity to lethal endotoxin shock was studied in male Holtzman rats. Sensitization to endotoxin shock accompanied conditions associated either with insulin secretion, viz., the fed state, treatment with intraperitoneal glucose, use of sulfonylurea β-cell stimulants, or with subcutaneous insulin. In contrast, endotoxin shock lethality was significantly reduced in situations of depressed insulin secretion, viz., either via fasting or mannoheptulose treatment. Glucose treatment did not sensitize rats to endotoxin shock when treatments with mannoheptulose and glucose were combined; this finding suggests that glucose sensitization to endotoxin shock was due to insulin secretion and not glucose per se. A critical role for insulin in the pathogenesis of endotoxin shock in the rat is indicated.

38. Effect of insulin on mitochondrial oxidative phosphorylation and energy charge of the perfused guinea pig liver. T. Ida, M. Sato, Y. Yamaoka, H. Takeda, Y. Kamiyama, K. Kimura, K. Ozawa, and I. Honjo. J. Lab. Clin. Med. 87: 925-933, 1976.

The effect of insulin was investigated in the isolated guinea pig liver perfused with Krebs-Ringer bicarbonate buffer containing red blood cells and albumin. In the mitochondria isolated from livers perfused with 10 units of insulin per hour, the phosphorylative activity with glutamate as a substrate increased to about 160% of control 60 min after the beginning of perfusion ($p<0.01$). Such an enhanced phosphorylative activity was accompanied by increases in the respiratory control ratio, state 3 respiration, and P/O ratio. On the other hand, in the liver perfused with insulin, the levels of the energy charge and adenine nucleotide quotient increased to a significant degree as compared to the liver without insulin ($p<0.01$ and $p<0.05$, respectively). It is suggested that insulin plays an important role as a portal factor in regulating mitochondrial oxidative phosphorylation and the levels of the phosphorylated adenine nucleotides.

39. Insulin resistance and its reversal by in vivo infusion of ATP in hemorrhagic shock. I. H. Chaudry, M. M. Sayeed, and A. E. Baue. Can. J. Physiol. Pharmacol. 54: 736-741, 1976.

Hemorrhagic shock in rats was produced by bleeding the animals to a mean arterial pressure of 40 mmHg, which was maintained for 2 hr. Muscles from these animals ('shock' muscles) demonstrated basal glucose uptake values unchanged from control values but, unlike the control muscles, the 'shock' muscles showed resistance to the stimulation of glucose uptake by insulin. Infusion of ATP-$MgCl_2$, ADP-$MgCl_2$, adenosine-$MgCl_2$, or GTP-$MgCl_2$ to animals following shock had no effect on basal glucose uptake; however, ATP-$MgCl_2$ but not the other nucleotides permitted insulin to exert its stimulatory effect on such muscles. An optimal insulin effect in ATP-$MgCl_2$ treated 'shock' muscles occurred at an insulin concentration of 0.001 U/ml, which is also the concentration required to produce optimal insulin effect in control muscles. Following 1-hr incubation in Krebs-HCO_2 medium, intracellular ATP contents of 'shock' muscles were about 50% lower than in control muscles. Treatment with ATP-$MgCl_2$ following shock, however, resulted in ATP contents in such muscles similar to those in control muscles. Possible mechanisms for this reversal of insulin resistance by in vivo infusion of ATP-$MgCl_2$ in shock are discussed.

40. Serologic modification of reticuloendothelial capacity and altered resistance to traumatic shock. J. E. Kaplan, T. M. Saba, and E. Cho. Circ. Shock 3: 203-210, 1976.

Reticuloendothelial system (RES) involvement in resistance to traumatic shock was evaluated through the utilization of rabbit anti-rat opsonic protein serum to effectively alter the plasma level of biologically active opsonic protein in order to induce selective impairment in reticuloendothelial (RE) phagocytosis. RE function was assessed by colloid clearance and opsonic activity was evaluated by an isotopic tissue bioassay technique. The shock model employed was the Noble-Collip drum (NCD) traumatic shock under anesthesia. After intravenous injection of antiserum at a dose of 1.0 ml/100 g body weight, there was a significant ($p<0.001$) depression of opsonin levels

within 15 min with a 76.8% decline in plasma activity by 30 min. The opsonin activity remained depressed at 60 min postinjection. RES phagocytic clearance dysfunction manifested a temporal lag behind the opsonic response with maximal depression ($p<0.005$) apparent at 60 min postantiserum injection as demonstrated by a 57% decrease in the global phagocytic index (K). Resistance to an LD_{50} traumatic shock was markedly attenuated after administration of antibodies to opsonic protein when evaluated both in terms of percentage of mortality as well as mean survival time ($p<0.01$). Normal rats succumbed at a rate of 55.2% with a mean survival time of 341 min, whereas antiserum-treated rats revealed a 100% mortality with a mean survival time of 117 min. The recent demonstration of hypo-opsonemia and coexistent RE failure in animals and humans after traumatic shock coupled with the present observations suggest a specific role for reticuloendothelial function in the genesis of refractory shock which may be mediated by opsonic deficiency after trauma.

41. Septicemia in the newborn due to gram-negative bacilli. Risk factors, clinical symptoms, and hematologic changes. U. Tollner and F. Pohlandt. Europ. J. Pediat. 123: 243-254, 1976.

The case histories of 17 newborns developing septic shock due to gram-negative bacilli were studied for pre- and perinatal risk factors, clinical symptoms, and hematologic changes. Immaturity, resuscitation procedures, and hypothermia on admission were found to be the risk factors most frequently preceding septicemia. A skin color fading and changing from reddish-pink to yellow-green was the most early noticeable clinical symptom in all patients. The total leukocyte counts as well as the relative proportion of bands increased significantly at the onset of illness. When septicemia advanced, a marked drop of leukocytes was found, while the relative proportion of bands increased further. Only 1 in 12 cases showed a decrease in the platelet counts at the height of septicemia. A procedure for the early diagnosis of a neonatal septicemia is proposed: (1) Registration of perinatal risk factors. (2) With perinatal risk factors a skilled and attentive clinical observation is necessary. Particular attention should be paid to changes of skin color. (3) White blood cell picture: (a) every day in patients with perinatal risk factors and (b) every 6 hr in patients showing suspicious symptoms.

42. Early diagnosis of neonatal bacteremia by buffy-coat examination. H. S. Faden. J. Ped. 88: 1032-1034, 1976.

This study demonstrates the value of the buffy-coat smear examination in the early diagnosis of neonatal bacteremia. It is inexpensive, easy to perform, and relatively efficient. In most situations large numbers of bacteria could be seen in each positive smear. Unfortunately, the presence of a positive buffy-coat smear was often associated with a poor prognosis; more than half (4 of 7) of infants with positive smears died.

43. Altered hepatic glycogen metabolism and glucoregulatory hormones during sepsis. R. T. Curnow, E. J. Rayfield, D. T. George, T. V. Zenser, and F. R. DeRubertis. Am. J. Physiol. 230: 1296-1301, 1975.

Levels of glucose, insulin, and glucagon in portal vein plasma and of liver glycogen and cyclic AMP and activities of glycogen synthase and phosphorylase in liver were assayed in control (CONT) rats and rats infected (INF) with Diplococcus pneumoniae. In INF rats compared with CONT rats, insulin and glucagon levels were higher (8, 12, 24 h). Activity of synthase I was lower (8, 12, 24 h) and of phosphorylase higher (12 and 24 h) in INF rats. Cyclic

AMP levels were higher in INF rats at 12 and 24 h. Total synthase activity was lower in INF rats at 24 h. Glucose given intravenously increased glycogen less in INF than in CONT rats and activated synthase and inactivated phosphorylase in all animals except at 24 h in INF rats. However, in situ perfusion of the livers at 24 h with glucose in buffer decreased phosphorylase activities in all animals and increased synthase I activities in CONT but not INF rats.

44. Defective neutrophil motility in hypovitaminosis D rickets. F. Lorente, G. Fontan, P. Jara, C. Casas, M. C. Garcia-Rodriquez, and J. A. Ojeda. Acta Paediatr. Scand. 65: 695-699, 1976.

The chemotactic activity and random motility of neutrophils, was studied in 38 patients with hypovitaminosis D rickets, and compared with 29 healthy controls of matched age. The chemotactic activity derived from the activated rickets serum as well as the amounts of the complement components C4, C3 and C5 was normal, but the cell motility was clearly defective ($p<0.001$). A possible relationship between defective neutrophil movement and the recurrent infections seen in these patients is suggested. The possible mechanisms responsible for the defect could be the alteration in Ca/P metabolism or a defective action of the vitamin D on the neutrophils.

45. Animal models of peritonitis. M. K. Browne and G. B. Leslie. Surg. Gynec. Obstet. 143: 738-740, 1976.

A reproducible animal model of peritonitis has been developed. It uses standard animals, standardized cultures of bacteria and simple techniques. Use of this model would facilitate comparison of data from workers in this field. The use of small rodents permits the use of comparatively large populations for statistical evaluation. The method is cheap and economic of laboratory space and does not require surgical expertise.

46. Coronary blood flow and reserve flow in canine hemorrhagic shock. K. van Ackern, U. B. Brückner, B. Hakimi, D. Opherk, J. Schmier, and I. Simo. Circ. Shock 3: 255-261, 1976.

Mongrel dogs anesthetized with morphine (1 mg/kg) and pentobarbital (15 mg/kg) were subjected to standardized hemorrhagic shock with reinfusion after spontaneous uptake of 35% of the bled volume. Determinations were made of coronary sinus flow (electromagnetic flow probe), cardiac output (thermodilution), coronary flow reserve (injection of dipyridamole) and arterial, venous, and coronary sinus pO_2 and pH. Except during the early stages following the initial hemorrhage when flow was decreased, coronary sinus flow increased steadily during the oligemic and reinfusion stages and returned to control flows and to levels about 50% above control in the later periods; only in the terminal stages did coronary flow fall to prehemorrhage values or slightly below. The intravenous injection of dipyridamole (0.2 mg/kg) resulted in an increase of coronary flow and a decrease of coronary vascular resistance in the control, oligemic, and reinfusion stages of shock, indicating the presence of "reserve" coronary flow. The increase of coronary flow with the concomitant rise of coronary sinus pO_2 and the presence of flow reserve even in late shock indicate that the decrease in cardiac function in hemorrhagic shock is not due to insufficient coronary blood flow to the myocardium. Our results suggest that a more likely cause is impaired O_2 utilization by the myocardium.

47. Effect of adrenaline on sugar transport in the perifused left atrium. I. Bihler and P. C. Sawh. Can. J. Physiol. Pharmacol. 54: 714-718, 1976.

The effect of adrenaline on the membrane transport of 3-methylglucose was studied in perifused isolated rat left atria that had been fully arrested. In this preparation a high concentration of adrenaline stimulated and a low one decreased sugar transport. The stimulatory effect was strongly inhibited by the β-adrenergic blocker propranolol and by the antilipolytic agent nicotinic acid. As the atria were not beating, the effects were not mediated by changes in the rate or strength of muscular contraction. The possible mechanisms of these effects of adrenaline on sugar transport are discussed.

48. Differences in the altered energy metabolism of hemorrhagic shock and hypoxemia. I. H. Chaudry, M. M. Sayeed, and A. E. Baue. Can. J. Physiol. Pharmacol. 54: 750-756, 1976.

The effect of hemorrhagic shock, hypoxemia, and anoxia on the levels of adenine and pyridine nucleotides of liver and kidney was assessed. ATP levels in liver and kidney of animals in shock or animals subjected to 7 min of anoxia decreased by 85 and 73%, respectively. Under hypoxic conditions (arterial pO_2 at 18 mmHg), the decrease was only 62 and 48% in liver and kidney, respectively. Tissue NAD levels decreased and NADH levels increased during shock but were found to be essentially unaltered during experimental hypoxemia. Thus, shock produced greater alterations in adenine and pyridine nucleotides than did hypoxemia alone, indicating that stagnant hypoxemia due to shock is more deleterious to energy metabolism than is severe hypoxemia with an otherwise normal circulation. The results also suggest that if an arterial pO_2 of 18 mmHg represents the initial stages of tissue hypoxia, then tissue ATP levels are a more sensitive indicator of this than NAD levels.

49. Reactive hyperemia: An index of the significance of coronary stenoses. W. S. Hillis and G. C. Friesinger. Am. Heart J. 92: 737-740, 1976.

Coronary arterial stenosis of varying severity and length were created in open-chest dogs. The reactive hyperemic responses (RHR) to 15 second occlusions were used to produce flow increases and judge the physiological significance of the narrowings. RHR are sensitive indices of functional impairment when resting flow is unchanged. It was demonstrated that the length as well as the severity is important in assessing physiological significance by evaluation of narrowings 3 to 9 mm long.

50. The perifused isolated left atrium: a preparation for studies on sugar transport in the myocardium. P. C. Sawh and I. Bihler. Can. J. Physiol. Pharmacol. 54: 708-713, 1976.

A procedure is described for the in vitro perifusion of the rat left atrium by recirculating medium through the atrial cavity and around the tissue, and for making the left atrium completely quiescent using surgical methods. The main advantage of this preparation is that it provides direct data on metabolic and transport processes in resting myocardium. Its use is illustrated by data on the time course, concentration dependence, insulin sensitivity and chemical specificity of the sugar transport system; in all these respects the resting left atrium resembles resting ekeletal muscle.

51. Heart failure and hypoglycemia. E. Colt. N. Y. St. J. Med. 76: 2033, 1976.

Hypoglycemia is well known in heart failure in infants, but appears to be less frequent and severe in adults. The patient reportedhere had unusually severe hypoglycemia associated with severe heart failure.

Liver-cell necrosis, poor dietary intake, and malabsorption must have contributed to this patient's hypoglycemia. In addition to the drugs already mentioned, he received small doses of pentazocine and propoxyphene, but only the latter, in very large doses, has been incriminated in the genesis of hypoglycemia. The 6-fold elevation of CPK may have been due to the severe congestive heart failure. Eschcar and Zimmerman found elevations of this enzyme in 7 of 27 patients with heart failure in the absence of myocardial infarction.

It would appear that in this patient hypoglycemia was just one of the protean manifestations of heart failure. Sweating, tachycardia, and confusion are prominent features of both these conditions. In view of the deleterious effects of hypoglycemia on myocardial function, this report suggests that frequent determinations of plasma glucose are indicated in patients with severe heart failure.

52. Changes in the interstitial fluid and the muscle water in rabbits in hemorrhagic shock. M. W. Wolcott, T. I. Malinin, and N. M. Wu. Ann. Surg. 184: 728-733, 1976.

Dynamics and changes in the biochemical composition in the interstitial fluid and the muscle water were studied in hemorrhagic shock. The interstitial fluid was collected from implanted perforated capsules. Muscle biopsies were examined with regard to their water content by the steady state magnetic nuclear resonance spectroscopy. The consistent and what appears to be the most significant changes were the fall in the interstitial fluid pressures, the quantitative reduction of muscle water, a sharp fall in the blood and interstitial blood pH, the moderate hyperkalemia and lack of change in blood and interstitial fluid sodium, and the rise in blood glucose levels not accompanied by a rise in the interstitial fluid glucose levels.

53. Hemodynamic effects of nitroprusside infusion during coronary artery operation in man. D. G. Lappas, E. Lowenstein, J. Waller, N. R. Fahmy, and W. M. Daggett. Circulation 54 (Suppl. III): 4-10, 1976.

The hemodynamic response to vasodilator therapy with sodium nitroprusside has been assessed in 33 patients with severe coronary artery disease (CAD) during coronary artery operation. The patients were divided into 3 groups: Group I included 7 patients with CAD and normal left ventricular filling pressure (LVFP<12 mmHg); Group 2 included 18 patients with CAD and chronic left ventricular (LV) dysfunction (LVFP>12 mmHg) and Group 3 included 8 patients with CAD and acute LV dysfunction (LVFP>12 mmHg) associated with an intraoperative hypertensive episode. Nitroprusside was administered intraoperatively at an initial infusion rate of 10-15 mcg/min and the rate was gradually increased thereafter until the criteria for effective therapy were satisfied. The effective dose ranged from 10-120 mcg/min with an average of 52±4 (SEM) mcg/min.

In all three groups, pulmonary and systemic arterial pressure, right and left ventricular filling pressure, and pulmonary systemic vascular resistance decreased significantly with nitroprusside infusion. Heart rate increased significantly in Group 1 and remained unchanged in Groups 2 and 3. Heart rate X systolic arterial pressure decreased significantly in Groups 1 and 3 and did not change in Group 2. Stroke index increased significantly in both groups of patients with elevated control LVFP (Groups 2 and 3) and remained unchanged in patients with normal left ventricular function (Group 1). Left ventricular stroke work index decreased in Group 1, increased in Group 2, and remained unchanged in Group 3. Right ventricular stroke work index decreased significantly in all groups.

These findings suggest that judicious intraoperative administration of sodium nitroprusside improves left ventricular function in patients with acute or chronic elevation of LVFP and LV dysfunction associated with severe CAD. Furthermore, nitroprusside is an effective drug for control of intraoperative hypertensive episodes in such patients.

54. Evaluation of the force-frequency relationship as a descriptor of the inotropic state of canine left ventricular myocardium. P. A. W. Anderson, J. S. Rankin, C. E. Arentzen, R. W. Anderson, and E. A. Johnson. Circ. Res. 39: 832-839, 1976.

The short-term force-frequency characteristics of canine left ventricular myocardium were examined in both isolated and intact preparations by briefly perturbing the frequency of contraction with early extrasystoles. The maximum rate of rise of isometric tension (F_{max}) of the isolated trabeculae carneae was potentiated by the introduction of extrasystoles. The ratio of F_{max} of potentiated to control beats (force-frequency ratio) was not altered significantly by a change in muscle length. However, exposure of the trabeculae to isoproterenol (10^{-7} M) significantly changed the force-frequency ratio obtained in response to a constant frequency perturbation. Similar experiments were performed on chronically instrumented conscious dogs. Left ventricular minor axis diameter was measured with implanted pulse-transit ultrasonic dimension transducers, and intracavitary pressure was measured with a high fidelity micromanometer. Atrial pacing was performed so that the end-diastolic diameters of the beats preceding and following the extrasystole could be made identical. Large increases in the maximum rate of rise of pressure (P_{max}) were seen in the contraction after the extrasystole. The ratio of P_{max} of the potentiated beat to that of the control beat was not changed by a 9% increase in the end-diastolic diameter, produced by saline infusion. Conversely, isoproterenol significantly altered this relationship in the same manner as in the isolated muscle. Thus, either in vitro or in situ, left ventricular myocardium exhibits large functional changes in response to brief perturbations in rate. The isoproterenol and length data indicate that the force-frequency ratio reflects frequency-dependent changes in the inotropic state, independent of changes in length.

55. Cardiac function and metabolism following hemorrhage in the newborn lamb. S. E. Downing, and J. C. Lee. Ann. Surg. 184: 743-751, 1976.

Cardiac performance was assessed in 33 lambs <1 to 5 days of age by means of left ventricular function curves. Performance was quantified by determining stroke volume ejected at end diastolic pressure 10 cm H_2O (SV_{10}) with constant afterload. Coronary flow, myocardial O_2 consumption (MVO_2), blood gas tensions and pH were determined. Measurements were obtained before and at 30 min intervals following hemorrhage to 30 mmHg arterial pressure, and in controls (arterial pressure 75 mmHg). Effects of metabolic acidosis,

hypercapnia and β-blockade were determined. In control lambs acidosis and hypercapnia failed to reduce SV_{10} after 2 hr. In hemorrhaged animals both factors sharply reduced SV_{10} and lambs with prior β-blockade showed no greater reduction. MVO_2 fell following hemorrhage but did not differ with metabolic conditions and did not relate to SV_{10}. It is concluded that β-adrenergic function is critically important in preserving left ventricular performance in newborn exposed to acidosis or hypercapnia. With sustained hemorrhage this mechanism fails leading to a significant depression of ventricular function. MVO_2 was not a determining factor in these studies.

56. Metabolic and other aspects of fever. K. E. Cooper, W. L. Veale, and Q. J. Pittman. Israel J. Med. Sci. 12: 955-959, 1976.

A currently accepted schema for the induction of fever by the endotoxins from gram-negative organisms, is as follows: the endotoxin (lipopolysaccharide pyrogen) interacts with circulating leukocytes and also with fixed cells of the reticuloendothelial system to which it is carried, causing these cells to elaborate and release another products known as endogenous pyrogen. Endogenous pyrogen is a polypeptide of relatively low molecular weight, and it is suggested that this substance is carried in the circulation to the hypothalamus where it possibly induces the synthesis of prostaglandins (PG) of the E series. The synthesized and released PG drive the thermoregulatory system in such a way as to increase heat production and decrease heat loss.

We have been suggesting that fever represents a pathological process, outside the ordinary thermoregulatory control mechanisms, which superimposes a drive on the heat-production and heat-conservation pathways. Further, our recent work has led us to suggest that there may be two mechanisms of fever--one related to the release of prostaglandins producing an initial rapid fever, possibly of short duration; and the second, due to the action of endogenous pyrogen at some other site in the brain, as yet undetermined and not dependent upon the PG mechanism.

57. Fever and leukocyte pyrogen. W. I. Cranston. Israel J. Med. Sci. 12: 951-954, 1976.

Though fever has been recognized for centuries as an accompaniment of inflammatory illness, it is only in the last 20 years or so that we have begun to have some idea of the way in which fever is produced, although some experimental work was carried out over a century ago. In 1875, Von Liebermeister concluded that in fever the body temperature was regulated at an abnormally high level, but that the thermoregulatory mechanism remained intact and efficient. This is a subject which is still a matter of controversy today. During the first 20 years of the present century, when i.v. injections of drugs and solutions were used increasingly in clinical practice, it was recognized that fever often followed such injections.

More and more confusing evidence is appearing in this field and it seems to me that we must either await an enormous improvement in technique or try to think out really critical experiments. Of course, logically, any hypothesis can only be disproved; it can never be firmly established.

58. Physiology and pathophysiology of glucagon. R. H. Unger and L. Orci. Physiol. Rev. 56: 778-826, 1976.

The islets of Langerhans perform the vital function of fuel distribution. The biologic actions of its two major secretory products, insulin and glucagon, endow it with the abilities to direct the storage of exogenous fuels in the

insulin-sensitive tissues of the body and, when required, to retrieve and redistribute them at rates precisely titrated to prevailing needs. The opposing and counterbalancing actions of the two hormones make possible wide changes in nutrient flux with but minor changes in their concentration.

Because in most higher life forms glucose is, under normal circumstances, the primary cerebral fuel, glucoregulation is the primary functional concern of the islet cell system. The A and B cells are exquisitely perceptive glucose sensors, responding promptly and appropriately to changes in glucose need and availability. Although they also respond to changes in the concentration of other substrates and hormones and to the autonomic nervous system, the ambient glucose concentration is the dominant controlling force of the bicellular unit and normally will determine the magnitude of the response to influential signals other than glucose.

In the moment-to-moment sense, insulin and glucagon can be viewed as directing the metabolic "traffic"; i.e., the flux of glucose, amino acids, fatty acids, and ketones. In the long-term sense, they may be regarded as determining the direction of metabolism toward anabolism or catabolism. Clearly, the properfunction of this organ is vital to health and to survival and its improper function may result in disorders to fuel delivery of which diabetes mellitus and hypoglycemia are familiar examples.

59. Lung defense mechanisms. M. Newhouse, J. Sanchis, and J. Bienenstock. New Engl. J. Med. 295: 990-998 (1st part); 1045-1052 (2nd part), 1976.

One of the most important functions of the lung, aside from its role in gas exchange and metabolism, is the provision of an essential biologic barrier between man and his environment. Of fundamental importance is the way in which the airways and lung parenchyma prevent entry of and neutralize or remove injurious agents, tasks performed so efficiently that the lung is normally sterile from the first bronchial division to terminal lung units.

The following topics are discussed in this two-part article: aerodynamic filtration, tracheobronchial secretions and mucociliary transport, macrophages, immunologic defenses.

60. Hyperinsulinism in endotoxin shock dogs. W. G. Blackard, J. H. Anderson, Jr., and J. J. Spitzer. Metabolism 25: 675-684, 1976.

Extreme hyperinsulinism was observed in endotoxin-shock dogs made hyperglycemic by glucose infusion. Qualitatively (at least in terms of gel filtration characteristics), the insulin secreted under these conditions was normal. Hyperinsulinism was not observed in endotoxin-shock dogs not given glucose. Thus hyperinsulinism does not explain the hypoglycemia so frequently observed in endotoxin-treated dogs.

Hyperinsulinism could not be explained by impaired degradation of insulin as disappearance of labeled insulin as well as cold insulin was comparable in control and endotoxin-treated animals. An adrenergic mechanism (either beta receptor stimulation or postadrenergic hyperresponsiveness of the beta cells) probably does not explain the hyperinsulinism observed in endotoxin-shock dogs given glucose as beta blockade failed to inhibit the hyperinsulinism.

Hyperinsulinism was not observed in endotoxin-shock dogs given tolbutamide. A tenfold rise in plasma IRG was observed in endotoxin-treated dogs whether glucose

was infused or not. The persistently low IRI levels in endotoxin-treated dogs not given glucose suggest that hyperresponsiveness of the beta cells to glucagon was not present in these animals.

Extreme hyperinsulinism in response to induced hyperglycemia in endotoxin-shock dogs is unexplained. Hyperresponsiveness of the beta cell to glucose during endotoxin shock seems likely.

61. The diagnosis and treatment of endotoxic shock. N. W. Lees. Anaesthesia 31: 897-909, 1976.

The management of a severe case of endotoxic shock is a prolonged and strenuous exercise. The initial aim is to achieve, as soon as possible, cardiorespiratory stability and control of the septic focus, thereafter, the provision of fluid and nutrition must be adequate. Constant observation is required so that swift action can be taken if complications such as hemorrhage or renal failure develop, or if there is failure to control the septic focus. The general welfare of the patient, with particular regard to general nursing care, reduction of the risk of secondary infection and reassurance also plays an important part. Efficient treatment requires an organised plan which covers all the relevant aspects and assigns priorities to the critical areas.

62. Isoproterenol, endotoxin shock and the generalized Shwartzman reaction. A. D. Collins, E. C. Henson, S. R. Izard, and J. G. Brunson. Arch. Path. Lab. Med. 100: 315-317, 1976.

Adult hybrid albino rabbits were divided into seven groups. Three groups were given two respective intravenous doses of 10, 25, or 100 µg of endotoxin at an interval of 24 hrs. Three other groups were given endotoxin as above, and in addition, were given 0.5 mg of isoproterenol hydrochloride (Isuprel) by subcutaneous injections at 8-hr intervals beginning at the time of the first injection of endotoxin. A single group was given isoproterenol only. The animals were observed for clinical signs of shock beginning at the time of the first injection of endotoxin. The mortality during the course of the experiment was noted. At the time of death, the animals were studied grossly, and sections were taken for light microscopy. Results showed no meaningful enhancement of endotoxin toxicity as manifested by shock, generalized Shwartzman reaction, or mortality.

63. An ultrastructural study of the mechanisms of platelet-endotoxin interaction. A. R. Spielvogel. J. Exptl. Med. 126: 235-249, 1967.

Electron microscopy has confirmed previous studies and has provided much new information on the mechanism of endotoxin-platelet interaction. The Boivin lipopolysaccharide preparation is particulate, and on electron microscope examination appears as a three-layered structure, morphologically similar to bacterial cell wall.

In vitro and in vivo experiments have demonstrated that these endotoxin particles adhere to platelets. In some species, particularly the rabbit, this is associated with loss of platelet contents, due to lysosomal and cell membrane lysis, resulting in platelet sphering and apparent cell death. Serial observation of degranulating platelets and metabolic studies indicate that although some platelet engulfment of endotoxin occurs, degranulation is not dependent upon phagocytosis.

Several observations suggest that these endotoxin effects are mediated through immune mechanisms:(1) Inactivation of complement in the suspending plasma by heating to 56°C, anticoagulation with EDTA, a reaction temperature of 5°C, ammonium hydroxide incubation, and adsorption with either zymosan or washed antigen-antibody complexes, inhibits both endotoxin adherence and platelet degranulation. (2) The reaction requires a plasma cofactor, possibly antibody, which can be adsorbed out by endotoxin. (3) Endotoxin adheres selectively to nonprimate platelets and primate red cells, a pattern conforming to immune adherence, a phenomenon requiring antigen, antibody, and complement.

It is suggested that endotoxin-induced platelet damage is dependent upon the intimate contact provided by immune adherence. We have not established whether degranulation is an endotoxin or complement effect. The species variation in susceptibility to endotoxin also merits further investigation.

64. Leukocyte phagocytic function and dysfunction. D. C. Hohn. Surg. Gynec. Obstet. 144: 99-104, 1977.

Although some species of bacteria are killed in vitro by humoral factors in cell-free serum, the in vivo experience with leukopenic patients illustrates the critical role played by phagocytic leukocytes in host resistance to infection.

Effective ingestion and killing of microorganisms requires the sequential and integrated function of the elements of the phagocytic system. Each step in the phagocytic process is also a potential crack in the armor of host defense, and an increasing number of clinically significant disorders of phagocytic function are being recognized and described.

The phagocytic leukocytes are equipped with a variety of intracellular microbicidal mechanisms which provide a degree of overkill capacity and allow these cells to meet the challenges posed by the many and varied microbial transgressors.

Undoubtedly, other phagocytic disorders will be discovered and other important aspects of the intraleukocyte killing mechanisms will be elucidated. For instance, little is known about the function of leukocytes within the relatively hypoxic environment of injured tissue where so many bacterial infections begin. As our understanding of phagocytic function develops, new ways may be found to augment host resistance by preservation or stimulation of the phagocytes.

65. Suppressed in vitro chemotaxis of burn neutrophils. J. B. Grogan. J. Trauma 16: 985-988, 1976.

A comparison of the chemotactic response of peripheral blood neutrophils between burn patients and control individuals was performed. Beginning approximately 5 days postburn a decreased chemotactic response of neutrophils from burned patients was noted. The most severely reduced chemotaxis was noted in the burn patients who died. No evidence of a burn serum factor which inhibited the chemotactic response of control neutrophils was found in this study.

66. Effects of indomethacin and nicotinic acid on E. coli endotoxin shock in anesthetized dogs. J. G. Hilton and C. H. Wells. J. Trauma 16: 968-973, 1976.

The effects of single and multiple doses of indomethacin and multiple doses of nicotinic acid upon Escherichia coli endotoxin shock were studied in mongrel dogs anesthetized with sodium pentobarbital. Survival, cardiac output, plasma volume loss, and mean arterial pressure were measured. Untreated animals did not survive

the procedure; animals treated with either multiple doses of indomethacin or nicotinic acid did survive for 5 hrs after endotoxin. Plasma volume losses of indomethacin and nicotinic acid treated animals were substantially less ($p<0.05$) than in untreated animals. Arterial pressures of indomethacin-treated animals were greater than that of either nicotinic acid treated or untreated animals. No differences in cardiac output were noted in surviving animals.

67. Expansion of interstitial fluid is required for full restitution of blood and volume after hemorrhage. J. C. Pirkle, Jr., and D. S. Gann. J. Trauma 16: 937-947, 1976.

Dogs with splenectomy and intact adrenals and adrenalectomized-splenectomized dogs infused with cortisol at a physiologically increased rate restored plasma volume and protein and demonstrated early extracellular hyperosmolality. In contrast, adrenalectomized-splenectomized dogs infused with cortisol at a rate did not restore volume or protein after a transient initial phase and did not demonstrate extracellular hyperosmolality.

From the foregoing evidence, it is postulated that the second state of restitution of blood volume following hemorrhage proceeds as follows:

1) Hemorrhage and the subsequent increase in plasma cortisol concentration lead to an increase in extracellular osmolality. An osmotic shift of intracellular fluid to the interstitium ensues.

2) The small increase in interstitial fluid volume results in a relatively large increase in interstitial hydrostatic pressure (because of the low compliance of the interstitium), thus accelerating lymphatic movement of interstitial protein to the vascular system. This movement results in a reequilibration of extracellular fluid toward the plasma.

3) The osmotically active agents mobilized by cortisol and hemorrhage do not appear to be glucose, sodium, or potassium.

4) There may be an adrenal factor other than cortisol that is necessary for full restitution of blood volume with 24 hrs after hemorrhage.

68. Detection of edema associated with myocardial ischemia by computerized tomography in isolated, arrested canine hearts. W. J. Powell, Jr., J. Wittenberg, R. A. Maturi, R. E. Dinsmore, and S. W. Miller. Circulation 55: 99-108, 1977.

This study was undertaken to determine if computerized tomography (CT scanning) with an EMI cranial scanner could detect edema associated with myocardial ischemia in canine hearts. A localized area of decreased density in the posterior papillary muscle and surrounding myocardium was detected on serial 8 mm CT scan slices of each heart after 60 min of circumflex artery occlusion and 45 min of reflow of blood. The wet/dry weight ratios and previous electron microscope studies of the ischemic posterior papillary muscles revealed edema accumulation. After 1 hr of arterial occlusion and 12 hr of reflow (which produces extensive necrosis and a decrease in the wet/dry ratio) lesions were still discernible but were less consistently as severe. Permanent ligation of the left anterior descending coronary artery and major collateral arteries for 6 hrs also resulted in a lesion of decreased density in the distribution of the occluded arteries.

Thus, CT scanning can detect, and is a potential means for sequential noninvasive quantitation of myocardial edema associated with ischemia.

69. Effects of sodium nitroprusside on left ventricular diastolic pressure-volume relations. B. R. Brodie, W. Grossman, T. Mann, and L. P. McLaurin. J. Clin. Invest. 59: 59-68, 1977.

The effect of sodium nitroprusside on the relationship between left ventricular pressure and volume during diastole was studied in 11 patients with congestive heart failure. Nitroprusside was infused to lower mean arterial pressure approximately 20-30 mmHg. High fidelity left ventricular pressures were recorded in all patients simultaneously with left ventricular cineangiography (biplane in 8 and single plane in 3 patients), allowing precise measurement of pressure and volume throughout the cardiac cycle. Left ventricular diastolic pressure-volume curves were constructed in each patient from data obtained before and during nitroprusside infusion. In 9 of 11 patients there was a substantial downward displacement of the diastolic pressure-volume curve during nitroprusside infusion, with left ventricular pressure being lower for any given volume with nitroprusside. Serial left ventricular cineangiograms performed 15 min apart in 6 additional subjects who did not receive sodium nitroprusside showed no shift in the diastolic pressure-volume relation, indicating that the shift seen with nitroprusside was not due to the angiographic procedure itself. A possible explanation for the altered diastolic pressure-volume relationships with nitroprusside might be a direct relaxant effect of nitroprusside on vascular smooth muscle. Alternatively, nitroprusside may affect the diastolic pressure-volume curve by affecting viscous properties or by altering one or more of the extrinsic constraints acting upon the left ventricle.

70. The intestinal mucosal lesions in shock. I. Studies on the pathogenesis. U. Haglund, T. Abe, C. Ahren, I. Braide, and O. Lundgren. Eur. Surg. Res. 8: 435-447, 1976. (For Part II, see Abstract #78.)

Mucosal lesions were produced in feline small intestine by evoking a simulated intestinal shock (local hypotension at 30 mmHg and stimulation of regional sympathetic vasoconstrictor nerves at 6 Hz for 2 h). The degree of mucosal damage was correlated to the level of intestinal blood flow. Microscopically characteristic lesions developed regularly in the small intestinal mucosa when intestinal blood flow was reduced below 12 ml/min x 100 g during the regional shock. The mucosal damage was graded histologically. No difference was found between untreated controls and cats in which the intestinal lumen was perfused with nitrogenated saline. Perfusion with oxygenated saline and i.v. injections of methylprednisolone on the other hand, prevented almost completely the development of the lesions. Albumin, activated charcoal and aprotinin instilled into the intestinal lumen reduced to some extent the mucosal damage. The obtained data support the view that hypoxia is the key factor in the pathogenesis of the mucosal lesions. However, epithelial and intraluminal enzymes are probably important contributing factors.

71. Inhibition of in vitro neutrophil chemotaxis and spontaneous motility by anti-inflammatory agents. I. Rivkin, G. V. Foschi, and C. H. Rosen. Proc. Soc. Exptl. Biol. Med. 153: 236-240, 1976.

A number of anti-inflammatory agents were tested for their effect on the chemotaxis responsiveness and on the spontaneous motility of neutrophils obtained from rabbit and rat peritoneal exudates and human blood. The majority of these agents, both steroidal and nonsteroidal, inhibited the chemotactic responsiveness of neutrophils obtained from all three sources to a bacterial chemotactic factor. The effective steroidal anti-inflammatory agents tested inhibited both

chemotaxis and spontaneous motility, whereas the nonsteroidal agents, with the exception of phenylbutazone, inhibited only chemotaxis and were without effect on motility.

72. Isolated perfused lung--substrate utilization. D. F. Tierney, S. L. Young, J. J. O'Neil, and M. Abe. Fed. Proc. 36: 161-165, 1977.

Lung metabolism has been extremely difficult to determine in vivo primarily because the lung is overwhelmed by a great blood flow that generally makes the Fick principle inadequate. Largely for reasons such as this, investigators have had to rely on in vitro preparations. The isolated perfused lung has the apparent advantage of being similar to the lung in vivo when compared with other preparations. For instance, there is evidence that the capillary bed of the lung may alter substrates and influence their subsequent metabolism. Substrates have contact with the capillary endothelium in isolated perfused lungs but not in tissue slices, homogenates or isolated cells. Our studies indicate that precursors of saturated phosphatidylcholine may include lipids, which are hydrolyzed in the capillary of the isolated perfused lung and thus become substrates such as free fatty acids, etc. However, tissue slices do not use the esterified lipids to the same extent, presumably because in this preparation the enzymes in the capillary endothelium do not have contact with the esterified lipids. Substrate utilization of the isolated perfused lung may be considerably altered by inflation of the lung or by pulmonary edema. Although glucose utilization and palmitate oxidation by the isolated perfused lung and by tissue slices of the rat lung are very similar, if the isolated perfused lung develops pulmonary edema, glucose utilization increases by nearly 100%. This phenomenon is apparently not due solely to fluid in the airspaces because in control studies with fluid added into the airways the glucose utilization did not increase to the degree observed with edematous lungs. Lung distention is associated with increased glucose consumption but marked distention is also associated with pulmonary edema. The effect of lung distension may be a direct effect or it may be secondary to the pulmonary edema.

73. Effect of starvation on muscle glucose metabolism: studies with the isolated perfused rat hindquarter. N. B. Ruderman, M. N. Goodman, M. Berger, and S. Hagg. Fed. Proc. 36: 171-176, 1977.

Studies in man and experimental animals suggest that the metabolism of glucose by skeletal muscle is depressed during starvation. To investigate the basis for this, the effect of starvation on the uptake and disposition of glucose in skeletal muscle was studied in the isolated perfused rat hindquarter. In contrast to earlier work carried out in heart, neither glucose uptake, whether stimulated by insulin or exercise, nor glycolysis were depressed by 48 hr of starvation or by perfusion of the hindquarter with acetoacetate, palmitate, or octanoate. Glucose oxidation, assessed from the oxidation of 1-[^{14}C]lactate, was depressed by ~75% in starved rats and by 30% in fed rats perfused with acetoacetate. Exercise increased lactate oxidation 10-fold in both fed and starved rats; however, the relative difference between the groups persisted. In general, changes in lactate oxidation were paralleled by changes in the activity of pyruvate dehydrogenase (active form). The data suggest that glucose metabolism in skeletal muscle is inhibited during starvation at the step of pyruvate oxidation and that this inhibition persists during exercise. They also suggest that the diminution of glucose uptake that occurs in skeletal muscle of intact organisms during starvation may not be related to the presence of high concentrations of free fatty acids and ketone bodies.

74. Serum protein concentration during hemorrhagic shock. L. C. Getzen, E. W. Pollak, and E. F. Wolfman, Jr. Surg. Gynec. Obstet. 144: 42-44, 1977.

Early changes in serum protein concentration during hemorrhagic shock were evaluated in a series of 20 dogs, following massive bleeding. The serum protein concentration fell faster than did the hematocrit value, with insignificant changes becoming apparent 15 minutes after hemorrhage, $p<0.05$. After this initial fall, a less marked descent occurred. The most remarkable changes were in the serum albumin fraction. Changes of the globulin levels were less evident. These findings of an early albumin loss, occurring within 15 minutes following acute massive hemorrhage in the dog, probably are due to a leakage of albumin into the interstitial space, secondary to increased capillary membrane permeability. Larger molecules, such as the globulin fraction, did not consistenlty decrease during the first 45 min following shock, a possible indication that loss of this protein into the interstitial space did not occur in a consistent manner. The aforementioned findings support the early use of intravenous infusions containing macromolecules, larger than albumin, during hemorrhagic shock, to re-establish an oncotic gradient, which is diminished due to a loss of albumin from the circulation.

75. Phagocytic and bactericidal activities of pulmonary macrophages following sublethal traumatic shock. P. W. Gudewicz, T. M. Saba, and F. Coulston. Proc. Soc. Exptl. Biol. Med. 153: 262-267, 1976.

The in vitro phagocytic and bactericidal responses of rat alveolar macrophages were investigated following sublethal traumatic shock. Phagocytosis of ^{14}C-labeled Pseudomonas aeruginosa by lung macrophages was elevated 1 hr post-trauma in the absence of bacterial opsonins. This response was transient with a return to normal by 24 hr. Bacterial phagocytosis by control and trauma alveolar macrophages was doubled in the presence of serum obtained either prior to or following trauma. In association with this acute phagocytic activation, resting O_2 consumption as well as bactericidal activity was stimulated in isolated alveolar macrophages harvested at 60 min post-traumatic injury. In contrast, the recoverable yeilds of lung macrophages following traumatic injury were significantly reduced at both the 1-hr and 24-hr postinjury period. Alveolar macrophage phagocytosis and metabolism are thus rapidly and transiently activated following host defense mechanisms following sublethal trauma. This response is in direct contrast to the previously documented acute depression of the hepatic Kupffer cell following traumatic shock and may represent a compensatory response of the lung RES during periods of hepatic RES dysfunction.

76. Control of A and B cells in vivo by sympathetic nervous input and selective hyper or hypoglycemia in dog pancreas. L. Girardier, J. Seydoux, and L. A. Campfield. J. Physiol. (Paris) 72: 801-814, 1976.

An extra-corporeal blood circuit was established between the cranial pancreatico-duodenal vein and the portal vein in the dog. Timed measurements of flow, hematocrit, insulin and glucogaon concentrations in this circuit were made in order to calculate the secretion rates of insulin and glucagon. The plasma glucose concentration in the pancreatico-duodenal vein was monitored at steady state from 50 to 330 mg/100 ml for periods of 70 min by infusing a saline solution or glucose into the cranio-pancreatico-duodenal artery. No change in peripheral glucose concentrations was detected.

1) When glucose concentration in the PD vein was lowered from 100 mg/100 ml to about 50 mg/100 ml, the basal insulin secretion rate was not modified. When the glucose concentration was increased from 100 mg/100 ml to about 300 mg/100 ml, the insulin secretion rate increased linearly over the range of concentrations tested.

2) Glucagon secretion rate was unmodified throughout the range of glycemia tested. Whereas net pancreatic glucagon secretion rate was not reduced by selective pancreatic hyperglycemia, it was reduced by systemic hyperglycemia at about the same concentration.

3) In atropinized pancreas, low frequency (2 Hz) electrical stimulation of the distal end of the ligated mixed pancreatic nerve caused a mean decrease of 44% in the secretion rate of insulin, and a mean increase of 42% in the secretion rate of glucagon at all PD vein glucose concentrations studied.

4) It can be concluded, therefore, that the sympathetic nervous input at physiological frequences controls the moment-to-moment secretory activity of the A and B cells of the pancreas independently of the concentrations of glucose.

77. Effects of angiotensin, vasopressin, and methoxamine on cardiac function and blood flow distribution in conscious dogs. G. Y. Heyndrickx, D. H. Boettcher, and S. F. Vatner. Am. J. Physiol. 231: 1579-1587, 1976.

A comparison was made of the effects of vasopressin (ADH), methoxamine (MX), and angiotensin II (AN) on coronary and left ventricular dynamics, cardiac output, and regional blood flow distribution in intact, conscious dogs. At an equal percent pressure elvation, ADH reduced cardiac output and cardiac rate the most, while AN had the least effect. After denervation of arterial baroreceptors, ADH still reduced heart rate, while AN increased it, suggesting nonbaroreceptor negative and positive chronotropic effects, respectively. A differential pattern on peak dP/dt was also observed, with ADH causing a greater reduction than MX while AN did not decreased dP/dt. With heart rate held constant, AN did not reduce dP/dt, suggesting a direct positive inotropic effect since dP/dt should have fallen slightly due to reflex mechanisms, as was observed with MX and ADH. LDH induced the greatest increase in coronary resistance (140%), while the least (46%) was observed with AN, which could be explained, in part, by the differential effects observed on cardiac rate and contractility. The greatest increase in resistance in the iliac bed occurred with ADH (307%), and the least with AN (34%). Conversely, the greatest constriction in the renal bed occurred with AN (95%), and lesser amounts were observed with ADH (36%) and MX (35%). Thus ADH, MX, and AN exert potent yet differential vasoconstricting actions on peripheral beds. In addition, while all three agents elicited coronary vasoconstriction, the differential effects on coronary vascular resistance appeared to be due predominantly to a difference in chronotropic and inotropic actions.

78. The intestinal mucosal lesions in shock. II. The relationship between the mucosal lesions and the cardiovascular derangement following regional shock. U. Haglund, T. Abe, C. Ahren, I. Braide, and O. Lundgren. Eur. Surg. Res. 448-460, 1976.

The relationship between the mucosal lesions in the gut, observed after a 2-hr period of regional hypotension, and the blood pressure fall seen after the hypotensive period was investigated in cats. Untreated controls were compared

to animals treated with intraluminal perfusion with nitrogenated or oxygenated saline or treated with intraluminal instillation of albumin, activated charcoal or aprotinin or i.v. injections of methylprednisolone. Untreated controls and cats perfused with nitrogenated saline exhibited a pronounced reduction in arterial blood pressure during the first posthypotensive hour. In the animals treated with methylprednisolone or perfused intraluminally with oxygenated saline only a small fall of blood pressure was observed. In the remaining groups of animals a moderate blood pressure reduction was noted. These results suggest a causal relationship between the intestinal mucosal damage and the posthypotensive cardiovascular derangement possibly via the release of cardiotoxic material from the hypoxic intestinal villi.

79. Deficits in reticuloendothelial humoral control mechanisms in patients after trauma. W. A. Scovill, T. M. Saba, J. E. Kaplan, H. Bernard, and S. Powers, Jr. J. Trauma 16: 898-904, 1976.

Plasma opsonic activity as expressed by an α-2-globulin which stimulates hepatic Kupffer cell phagocytosis, and thus modulates RES clearance, was determined in patients at varying intervals following whole-body trauma. Plasma opsonic actitivy decreased markedly following trauma in both nonsurviving (NS) and surviving (S) trauma patients as compared to an age- and sex-matched group of healthy volunteers. The initial post-traumatic hypoopsonemia (0-72 hr) was more severe ($p<0.01$) in nonsurviving patients than surviving patients. Survivors following trauma manifested restoration of opsonin levels with a definite transient rebound hyperopsonemia during the recovery phase (11-30 days); nonsurviving patients exhibited persistent systemic α-2-globulin opsonic deficiency. On the basis of previous animal and human studies, the presently observed humoral deficits following trauma in patients could contribute to impairment of reticuloendothelial Kupffer cell clearance of blood-borne particulate matter such as fibrin, damaged platelets, and other altered autologous tissue. The importance of post-trauma RES dysfunction to survival following severe injury warrants further investigation and clinical consideration.

80. Differentiation between endogenous pyrogen and leukocytic endogenous mediator. C. A. Mapes and P. Z. Sobocinski. Am. J. Physiol. 232: C15-C22, 1977.

The crude material released from glycogen-stimulated rabbit peritoneal polymorphonuclear leukocytes when administered to experimental animals elicits a number of metabolic and physiologic alterations characteristic of those observed in the host inflammatory response. Classically, the mediator of febrile response observed in rabbits and other species has been termed endogenous pyrogen (EP), whereas leukocytic endogenous mediator (LEM) has been used as a general term to denote the substance(s) mediating multiple inflammatory responses observed in rats. The latter substance, however, has not been previously demonstrated to differ from EP. This report presents evidence indicating that EP and LEM are different molecular species. Evidence supporting the differentiation between these entities includes: physical separation of EP from one or more mediators that induce metabolic alterations attributed to LEM; production of LEM activities by stimulated polymorphonuclear leukocytes in the absence of detectable pyrogenic activity; and differences in the release of EP and LEM from stimulated rabbit granulocytes in the presence of potassium ion.

81. Hepatic cell integrity in hypodynamic states. R. P. Carlson and A. M. Lefer. Am. J. Physiol. 231: 1408-1414, 1976.

Changes in liver integrity were studied in isolated perfused cat livers during simulated shock conditions (i.e., combined hypoxia, acidosis, and ischemia) or under the influence of each hypodynamic state separately. The combined hypodynamic stimuli depressed carbon clearance 51% and significantly elevated lactic acid dehydrogenase (LDH) and cathepsin D activities in the perfusate. The perfused liver was more seriously affected by hypoxia than by acidosis or ischemia alone. Reticuloendothelial clearance was depressed 20% and 25% in acidosis and hypoxia, respectively. Hypoxia also induced a 3-fold increase in cathepsin D and a 13-fold increase in LDH activities in the perfusate. After 150 min of hypoxia or ischemia, free cathepsin D in liver tissue increased significantly. The impairment of liver cell integrity (i.e., of Kupffer and parenchymal cells) occurred between 60 and 90 min during simulated shock conditions, indicating that the liver is stable for 60 min when it is exposed to hypoperfusion. The perfused liver is sensitive to local stimuli that predominate in circulatory shock, particularly hypoxia. These stimuli promote the release of lysosomal and cytoplasmic enzymes as well as depress phagocytosis by the reticuloendothelial system, phenomena that exacerbate the shock state.

82. Effects of intravenous anesthetic agents on left ventricular function in dogs. L. D. Horwitz. Am. J. Physiol. 232: H44-H48, 1977.

The cardiovascular effects of ketamine hydrochloride and thiopental sodium were studied in 11 dogs. During anesthesia, mean heart rate rose to 185 beats/min with ketamine and 147 beats/min with thiopental. Cardiac output was increased with ketamine but unchanged by thiopental. The maximum first derivative of the left ventricular pressure (dP/dt max) fell by 14% with thiopental but did not change significantly with ketamine. Propranolol resulted in attenuation of the tachycardia and a fall of 10% in dP/dt max with ketamine but had little effect on the response to thiopental. Phentolamine had no consistent effects on either drug. With pentolinium both drugs decreased dP/dt max. Intracoronary injection of ketamine decreased dP/dt max. Adrenalectomy had little effect on the responses to either anesthetic. The results lead to the conclusion that both ketamine and thiopental have myocardial depressant effects, but, whereas thiopental does not alter sympathetic tone, the depressive effects of ketamine are obscured by stimulation of cardiac sympathetic nerves.

83. Measurement of intrarenal anatomic distribution of krypton-85 in endotoxic shock in dogs. J. C. Passmore, R. E. Neiberger, and S. W. Eden. Am. J. Physiol. 132: H54-H58, 1977.

Renal blood flow distribution was measured in control dogs and dogs in endotoxic shock by utilizing a modifiction of ^{85}Kr washout. Kidneys, injected with ^{85}Kr via a renal arterial cannula, were removed at several specific intervals after injection, rapidly frozen, and sectioned transversely so that pieces of tissue could be isolated and counted for radioactivity. Control outer cortical blood flow was 462 ml/min per 100 g tissue wt, but 122 ml/min per 100 g during shock. Control inner cortical outer medullary flow was 396 ml/min per 100 g but 166 ml/min per 100 g in shock. Control flow in the inner stripe of the outer zone of the medulla was 130 ml/min per 100 g and 134 ml/min per 100 g in shock. In shock the initial volume of radioactivity distributed to outer cortex was smaller, to inner cortex the same, and to inner stripe outer zone of the medulla larger than in controls. This study delineates renal washout of ^{85}Kr from

specific areas of the kidney and indicates the alterations in extent and magnitude of this washout in endotoxic shock.

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