AD-A035 622 OKLAHOMA UNIV HEALTH SCIENCES CENTER OHLAHOMA CITY D--ETC F/G 6/5
ABSTRACT REFERENCE LIST: REVIEWS OF PERTINENT LITERATURE IN SHO--ETC(U)
NOV 76 L B HINSHAW N00014-76-C-0229
UNCLASSIFIED TR-113 NL

1 OF 1
ADA035622

END

DATE
FILMED
3-77

OFFICE OF NAVAL RESEARCH

Contract N00014-76-C-0229

Project NR 105-516

TECHNICAL REPORT NO. 113

See 1473 in back

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

29 November 1976

OFFICE OF NAVAL RESEARCH

Contract N00014-76-C-0229

Project NR 105-516

TECHNICAL REPORT NO. 113

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

29 November 1976

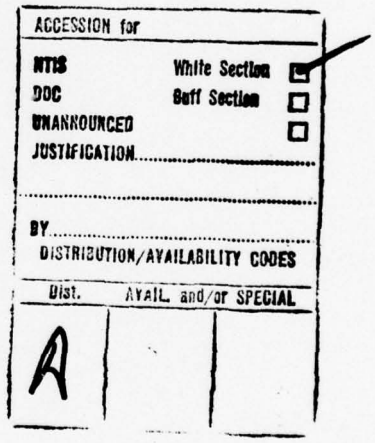

TABLE OF CONTENTS

32. MYOCARDIAL OXYGEN AVAILABILITY AND CARDIAC FAILURE IN HEMORRHAGIC SHOCK.
J. C. Lee and S. E. Downing.
Am. Heart J. 92: 201-209, 1976 15

33. STUDIES OF THE ABSORPTION AND METABOLISM OF GLUCOSE FOLLOWING INJURY. THE SYSTEMIC RESPONSE TO INJURY.
J. M. Howard.
Ann. Surg. 141: 321-326, 1955 15

34. DECLINE IN PANCREATIC INSULIN RELEASE DURING HEMORRHAGIC SHOCK IN THE BABOON.
G. S. Moss, G. Cerchio, D. C. Siegel, P. C. Reed, A. Cochin, and V. Fresquez.
Ann. Surg. 175: 210-213, 1972 16

35. SERUM INSULIN RESPONSE IN HEMORRHAGIC SHOCK IN BABOONS.
G. S. Moss, G. M. Cerchio, D. C. Siegel, P. A. Popovich, and E. Butler.
Surgery 68: 34-39, 1970 16

36. INSULIN RESPONSE DURING HYPOVOLEMIC SHOCK.
W. E. Bauer, S. N. M. Vigas, R. E. Haist, and W. R. Drucker.
Surgery 66: 80-88, 1969 16

37. PANCREATIC BLOOD FLOW AND INSULIN OUTPUT IN SEVERE HEMORRHAGE.
T. S. Lau, W. Taubenflígel, R. Levene, G. Farago, H. Chan, I. Koven, and W. R. Drucker.
J. Trauma 12: 880-884, 1972 17

38. EXPERIMENTAL STUDIES ON COAGULATION-FIBRINOLYTIC ACTIVITY OF WHITE BLOOD CELLS INFLUENCED BY ENDOTOXIN.
N. Sakuragawa, K. Takahashi, M. Yoshiyama, C. Jimbo, K. Niiya, M. Matsuoka and Y. Ohnishi.
Thromb. Res. 8: 887-891, 1976 17

39. STUDIES ON PLASMA INSULIN LEVELS IN THE POSTTRAUMATIC PHASE IN RABBITS.
J. P. N. Chansouria, A. K. Singh, K. N. Udupa.
J. Trauma 13: 1063-1065, 1973 17

40. INSULIN RESISTANCE IN EXPERIMENTAL SHOCK.
I. H. Chaudry, M. M. Sayeed, and A. E. Baue.
Arch. Surg. 109: 412-415, 1974 17

41. EFFECT OF SURGICAL PITUITRIN UPON PORTAL AND HEPATIC CIRCULATION.
I. Heimburger, S. Teramoto, and H. B. Shumacker, Jr.
Surgery 48: 706-715, 1960 18

42. EFFECTS OF SODIUM PENTOBARBITAL ANESTHESIA ON LEFT VENTRICULAR FUNCTION AND DISTRIBUTION OF CARDIAC OUTPUT IN DOGS, WITH PARTICULAR REFERENCE TO THE MECHANISM FOR TACHYCARDIA.
W. T. Manders and S. F. Vatner.
Circ. Res. 39: 512-517, 1976 18

1. Pulmonary and systemic capillary permeability to protein following endotoxin. W. F. Northrup III and E. W. Humphrey. Surg. Forum 27: 65-67, 1976.

Although it is well known that endotoxin increases permeability in systemic capillaries, the data on its effect in pulmonary capillaries are conflicting. This experiment was designed to define pulmonary and systemic capillary lymph/plasma concentration ratios (C_l/C_p) and fluxes of native albumin (J_{alb}) and globulin (Jglob) in the right (RTD) and left thoracic ducts (LTD) of dogs given endotoxin, and to compare the results with previous similar experiments following hemorrhagic shock and reinfusion.

With an increase in fluid flow across the capillary membrane secondary to a change in hydrostatic pressure, a sieving effect should occur in which there is a decrease in the concentration of protein in lymph. With an increase in permeability of the capillary membrane to protein, there should be an increase in the lymph to plasma concentration ratio for protein. These data suggest that endotoxin shock of this magnitude produces a different response in pulmonary and systemic capillaries from that previously reported for hemorrhagic shock. Hemorrhagic shock caused a 10-fold increase in Q_{rtd} but a minimal increase in Q_{ltd}. Endotoxin caused a short-lasting increase in Q_{rtd} but a 5-fold to 6-fold increase in Q_{ltd} that continued for a prolonged period. With hemorrhagic shock, the increase in C_l/C_p for albumin and globulin was greater in the RTD than in the LTD, but with endotoxin, the increase in this ratio was greatest and occurred earliest in the LTD.

2. Prolonged moderate hypothermia and experimental endotoxin shock. R. L. Engle, and R. D. Rink. J. Surg. Res. 21: 7-16, 1976.

An unanesthetized, chronically cannulated rat shock model has been presented, and the effects of hypothermia on survival and various parameters have been assessed. The results indicate that prolonged moderate hypothermia is of benefit in endotoxic shock. Lengthened survival of eventual fatalities suggests that moderate hypothermia also provides increased time for the use of traditional therapeutic measures. The data have been collected in a manner that clarifies the specific role of moderate hypothermia in extending survival, and the unanesthetized shock model presented should provide a convenient model for further metabolic and physiologic studies.

3. Effects of THAM, isoprenaline and propranolol on blood flow and vascular resistances of the liver after in- and outflow occlusion. E. Stoitchcov, T. Kawai, F. Bleser and R. Benichoux. Eur. Surg. Res. 8: 211-226, 1976.

The responsibility of the portal and the hepatic artery circulations during shock states has been established by studying the effects of a 15- min occlusion of two of the following blood vessels on 23 dogs: inferior vena cava below the diaphragm, portal vein and hepatic artery. Intrahepatic vascular resistances were computed from blood pressure records in these vessels and transhepatic blood flow studies using the ^{133}Xe clearance method. The animals were treated with THAM, plasmagel, isoprenaline, and propranolol. The tolerance of the occlusion is significantly improved when the animals are treated with the association of the four drugs. The portal and the systemic arterial blood pressures return to normal more promptly. Sinusoid and peribiliary resistances are remarkably stable if compared to the changes

occurring in the control animals. The well-known benefit of THAM is improved by the apparently paradoxical association of isoprenaline and propranolol. In fact, at the doses which have been used, they counterbalance their mutual disadvantages. Finally, the analysis of the hepatic blood flow rates and vascular resistances suggests that the splanchnic shock has two components: hepatic and visceral.

4. Microcirculatory approach to the treatment of circulatory shock with a new analog of vasopressin, [2-phenylalanine, 8-ornithine] vasopressin. B. M. Altura. J. Pharm. Exptl. Ther. 198: 187-196, 1976.

Pressor amine therapy in circulatory shock has been generally unfavorable, presumably because these drugs produce unselective, intense vasoconstriction and curtail rather than improve true capillary inflow, distribution and outflow in the microcirculation. The present study compares the influence of a new analog of vasopressin, [2-phenylaline,8-ornithine]vasopressin (POV), over wide dose ranges and Ringer's solution on: 1) survival after circulatory shock, induced by different means (e.g., hemorrhage, bowel ischemia); 2) blood pressure and hematocrit in shocked animals; and 3) various microcirculatory parameters after induction of hemorrhage and bowel ischemia shock (e.g., lumen diameters of various types of microvessels, reactivity of microvessels, microvascular flow patterns, leukocytic sticking, petechial hemorrhage formations, vasomotion, etc.). Local administration of POV, in contrast to constrictor catecholamines, induces a venular-to-arteriolar profile of constrictor activity in the normal rat mesenteric microcirculation. Systemic administration of POV to rats subjected to either lethal hemorrhage or bowel ischemia shock: 1) increases survival rates 2- to 8-fold over control rats receiving Ringer's solution; 2) produces a plateau-like effect on arterial blood pressure and returns arterial hematocrits toward normal after hemorrhage; and 3) regenerates and sustains vasomotion and venular tone, decreases microvascular hyperreactivity characteristic of shock syndromes, restores constricted arteriolar lumen sizes toward normal, predisposes to a splanchnic microbed virtually free of stasis and petechiae, and restores capillary perfusion and outflow to near-normal. These findings indicate that it is possible to synthesize vasoactive molecules which exert selective microvascular effects and are highly beneficial in therapy of low-flow states.

5. Hemodynamic effects of steroids in cardiac disease. L. Gould, C. V. R. Reddy, C. R. N. Swamy, W. Chua, and J.-C. Dorismond. Am. Heart J. 92: 133-138, 1976.

The hemodynamic effects of intravenous methylprednisolone were documented by right heart catheterization in 7 patients with an acute uncomplicated transmural myocardial infarction 1 to 9 days after the onset of symptoms. Intracardiac pressure, brachial artery pressure, and cardiac output were determined before and 1 hour after the termination of the methylprednisolone infusion. Two grams of methylprednisolone were infused over a 20-min period. The brachial pressure rose from a mean of 82 to 90 mmHg (NS). The brachial artery mean pressure fell in the one patient with a 1-day-old infarction, and it rose in the 6 patients with an older infarction, from 83 to 94 mmHg ($p<0.01$). As the brachial artery pressure rose in one patient, chest pain and marked ST-segment elevation occurred which were relieved by nitroglycerin. This experience promoted us to terminate the steroid study.

There was a nonsignificant increase in the cardiac index and wedge pressure. The raise in the brachial artery pressure with an infarction older than 1 day was an unexpected finding, since steroids are presumed to be vasodilating agents.

6. Endotoxin shock in the dog. Alterations in hemodynamic and hematologic parameters during bolus and infusion studies. O. Petrucco, P. S. Rao, and D. Cavanagh. Am. J. Obstet. Gynec. 114: 1060-1065, 1972.

Endotoxin shock still acounts for a large number of deaths in association with pregnancy despite the increased usage of newer and more potent antibiotics. Not uncommonly, the clinical picture is complicated by the development of acute renal failure, the pathogenesis of which remains debatable. The present study was undertaken to investigate further the changes in hemodynamics which occur in dogs when endotoxin is administered either as a bolus or by continuous infusion. In addition, because it is possible that deposition of fibrin, platelets, and white blood cells within the renal microcirculation could be responsible for, or contribute to, the increase in vascular resistance within the kidney, these parameters were monitored, and histologic evidence of intravascular coagulation was sought.

Alterations in mean aortic pressure, central venous pressure, renal vein pressure, and renal artery flow were studied following endotoxin administration in the dog. Following the administration as an intravenous bolus, a fall in mean aortic pressure, a fall in renal artery flow, and a concomitant rise in renal venous pressure were demonstrated. The observed decrease in platelet and white cell counts was found to be similar in aortic and renal vein blood. The hemodynamic and hematologic findings were similar when endotoxin was given in a 6-hr infusion. Fibrin deposition could not be demonstrated by histologic means in kidney, liver, or lung tissue in animals receiving endotoxin as a bolus or as an infusion of up to 6 hours.

7. Fine structural changes in myocardial ischemic injury. R. B. Jennings, J. H. Baum, and P. B. Herdson. Arch. Path. 79: 135-143, 1965.

Fine structural changes in dog myocardium associated with periods of ischemia known to cause reversible or irreversible injury were investigated and compared with the appearance of nonischemic control myocardium. Reversible changes, induced by coronary occlusion lasting for 15 minutes or less, included moderate relaxation of myofibers, margination of nuclear chromatin, moderate glycogen depletion, and occasional mitochondrial abnormalities. Changes observed in myocardial cells irreversibly injured by ischemia lasting 30 minutes or longer included extreme relaxation of myofibers, marked margination of nuclear chromatin, a virtual absence of glycogen, and extensive mitochondrial abnormalities. Intramitochondrial granules, which may represent accumulations of calcium, became increasingly prominent with more prolonged ischemia.

8. Failure of nicotinamide in the treatment of hemorrhagic shock. I. H. Chaudry, S. Zweig, M. M. Sayeed, and A. E. Baue. J. Surg. Res. 21: 27-32, 1976.

Hemorrhagic shock in rats was produced by bleeding the animals to a mean arterial pressure of 40 mmHg which was maintained for 1.5 hr. ATP, ADP, and NAD (nicotinamide adenine dinucleotide) levels decreased and NADH (reduced pyridine nucleotide) levels increased significantly in liver and

kidney of such animals. Infusion of NAD, nicotinamide, or nicotinic acid following shock increased the tissue NAD and decreased the NADH levels. Under ideal conditions, the oxidation of NADH to NAD should result in phosphorylation of ADP. Thus more ATP would be expected to be present. However, infusion of the above compounds failed to affect the tissue ATP levels after shock. Failure of animals to survive shock despite increases in tissue NAD levels following NAD, nicotinamide, or nicotinic acid infusion suggests that these infusions have no salutary effect in hemorrhagic shock.

9. Total body washout for the treatment of endotoxin shock. An experimental study. Y. Nakamura, A. Wakabayashi, T. Woolley, P. Mullin, Y. Ito, and J. E. Connolly. Arch. Surg. 111: 783-786, 1976.

In order to study the therapeutic effects of total body washout (TBW) in experimental endotoxin shock, we used the following procedure. Seventeen rabbits (controls) received Escherichia coli endotoxin (5 mg/kg) intravenously and were observed for 12 hours. Shock developed in 14 rabbits; they died in 5.2±1.0 (mean±SD) hours, with a survival rate of 18%.

Seventeen rabbits were subjected to TBW only. Muscle temperature was lowered to 25°C with a pump oxygenator circuit and the animals were exsanguinated. After residual blood was flushed out with cold, lactated Ringer solution, the animals were rewarmed with another circuit that was primed with homologous blood. Fourteen animals survived (82%).

Two hours after E. coli endotoxin was injected intravenously, 17 animals were treated with TBW. The survival rate (53%) of this group was significantly higher than in the control group (18%) ($p<.005$). Eight nonsurvivors showed hypotension and acidosis even after TBW treatment, thus indicating the irreversibility of their endotoxin shock.

This study indicates that endotoxin shock may be reversed by TBW if it is instituted before irreversible cellular damage.

10. Abolition of endotoxin tolerance: effect on circulating leukocytes. J. C. Herion, W. B. Herring, R. I. Walker, and J. G. Palmer. Am. J. Physiol. 215: 811-816, 1968.

Tolerant animals given the same dose of endotoxin as nontolerant ones develop less fever, less granulocytopenia at 1 hr, and earlier appearance of granulocytosis. In animals tolerant to 10 µg/kg (maximal pyrogenic dose) progressively larger doses evoke proportionately more fever until the maximum reappears following 500 µg/kg; it takes 1,000 µg/kg, however, before granulocytopenia reappears at 1 hr. Animals tolerant to 2 µg/kg show no increase in fever with doses of 200 µg/kg or less but 300 µg/kg both abolishes febrile tolerance and produces granulocytopenia gain at 1 hr. Since all tolerant animals clear labeled endotoxin faster than non-tolerant animals this suggests that within limits, those tolerant to small doses appear to detoxify endotoxin better than those tolerant to large doses. In animals made tolerant to 2 µg/kg and given Thorotrast to abolish tolerance, endotoxin is cleared more slowly even than in nontolerant animals. In these animals 2 µg/kg evokes the same changes in fever and circulating leukocytes as 200 µg/kg in those not given Thorotrast. Thus the magnitude of fever and leukocyte responses may be related to the amount of endotoxin circulating early after injection.

11. The effect of hemorrhagic shock on disseminated intravascular coagulation. R. M. Hardaway, R. S. Dixon, E. F. Foster, B. L. Karabin, F. D. Scifres, and T. Meyers. Ann. Surg. 184: 43-45, 1976.

It has been shown that pure hemorrhagic shock, unaccompanied by any other factor, is nearly always reversible in dogs even though the mean arterial pressure is kept at 40 mmHg for 4 hours or longer. The reason that the usual Wiggers hemorrhagic shock is fatal after 2 to 4 hours is that the returned blood is altered by its exposure in the reservoir and when returned to the animal, results in irreversible shock and death. If the blood is carefully bled through a short, plastic catheter into a closed blood bag, the dog will survive. The cause of death in so-called "irreversible" hemorrhagic shock is not the hemorrhagic shock, per se, but the return of the altered blood to an animal in a shock state.

Experiments tend to confirm the hypothesis that a thromboplastic substance in the blood stream causes little DIC if blood flow is normal. However, if the same quantity of thromboplastic material is present in a slow capillary flow, it will produce DIC and possible death, with a marked clotting defect.

12. Use of Limulus lysate for detecting gram-negative neonatal meningitis. D. Dyson and G. Cassady. Pediatrics 58: 105-109, 1976.

The Limulus lysate test was evaluated as a method for rapid detection of neonatal gram-negative bacterial meningitis. A total of 208 CSF samples were collected from 145 newborn infants suspected of having meningitis. Initial samples from all 6 babies with culture-proven gram-negative bacterial meningitis had positive Limulus tests within 30 min of incubation. Samples from 14 infants with gram-negative organisms isolated only in blood and/or urine as well as from 4 neonates with gram-positive organisms in CSF cultures and from 13 with gram-positive organisms in blood cultures all yielded negative Limulus test.

Thus, of 27 newborn infants with bacteria demonstrated in systemic cultures, only those 6 with gram-negative organisms in CSF had positive CSF Limulus tests. The CSF Limulus test was shown to be a rapid, reliable, and specific test for the detection of neonatal gram-negative bacterial meningitis.

13. Neonatal hypoglycemia revisited, 1975. R. L. Gutberlet and M. Cornblath. Pediatrics 58: 10-17, 1976.

Between 1971 and 1973, the frequency of neonatal hypoglycemia was 4.4/1,000 total inborn live births or 15.5/1,000 low-birthweight infants. During that same time, of 257 transferred infants, 13 or 5.1% were hypoglycemic. The hypoglycemic manifestations differed between the inborn and outborn infants as well as from those previously described for transient symptomatic hypoglycemia. This required a new classification for low blood glucose values in the neonate, based on intrauterine nutrition, stress, symptoms, and underlying pathology. Four categories were defined: category I: early transitional hypoglycemia; category II: secondary hypoglycemia; category III: classical transient hypoglycemia; and category IV: recurrent, severe hypoglycemia. One outborn infant was in the latter group due to β-cell hyperplasia and was only cured after a 90% pancreatectomy.

Data revealed that early treatment of perinatal asphyxia was associated with a decreased frequency of hypoglycemia. While not a prospective survey, the evidence suggested that current neonatal intensive care may decrease the frequency of transient symptomatic neonatal hypoglycemia.

14. Hypoglycemia in small-for-dates newborn infants. R. de Leeuw and I. J. de Vries. Pediatrics 58: 18-22, 1976.

In 24% (18 out of 76) small-for-dates a "significant" though asymptomatic hypoglycemia was demonstrated during the first 6 hours of life. The cord blood glucose concentration was lower in the hypoglycemic compared to that of the small-for-date normoglycemic group. In the hypoglycemic infants, the disappearance rate of glucose was significantly elevated and the lipid mobilization disturbed. It is suggested that a lack of lipids for energy metabolism increases the glucose expenditure and hence increases the risk for hypoglycemia.

An adequate noenatal lipid mobilization and combustion contribute to glucose homeostatis. This may be the explanation for the fact that not all small-for-dates newborn infants become hypoglycemic after birth. The low glycogen content of the liver puts these infants at risk for neonatal hypoglycemia. An extremely low content of body fat and/or a disturbed neonatal lipid mobilization are factors (among others) that increase the risk for hypoglycemia in small-for-dates infants. In the absence of lipids for energy metabolism the expenditure of glucose increases and the depot of glycogen is exhausted earlier, resulting in hypoglycemia.

15. Effect of intravenous hyperalimentation on established delayed hypersensitivity in the cancer patient. E. M. Copeland, B. V. Mac Fadyen, Jr., and S. J. Dudrick. Ann. Surg. 184: 60-64, 1976.

Those patients who are immunocompetent at the outset of oncologic therapy have better regression of malignant disease and longer survival free of malignant disease than do those patients who are immunologically incompetent. No doubt multiple factors affect immunocompetence, and one of these is nutrition. Law and co-workers have demonstrated that function of several immunological parameters returned after malnourished human beings or animals were nutritionally repleted. Since antibodies must be manufactured and sensitized lymphocytes must be produced, adequate building blocks in the form of amino acids, minerals, vitamins and energy in the form of glucose should be available for proper function of the immune system.

Forty-seven cancer patients were selected for study based on their candidacy for hyperalimentation. Each patient received selected skin test antigens intradermally in the forearm prior to the initiation of hyperalimentation, and at 7-day intervals throughout treatment with either chemotherapy, radiation therapy or surgery. Of 23 patients who received chemotherapy, 17 initially had negative skin tests. Thirteen of those patients had positive skin tests after an average of 11.4±5.5 days of hyperalimentation. Response to chemotherapy occurred only in those patients whose skin tests were positive, and conversion of skin test reactivity to positive occurred before clinical regression of metastatic disease. No patient who received radiation therapy developed or retained positive skin test reactivity, although nutritional repletion was considered satisfactory in each patient.

Surgical patients whose skin tests converted to positive or remained positive preoperatively had an uncomplicated postoperative recovery, whereas 2 of 4 patients whose skin tests remained negative expired post-operatively. Absence of established delayed hypersensitivity in the cancer patient who is treated with chemotherapy or surgery is probably secondary to generalized malnutrition, and established cell-mediated immunity can be restored by proper nutritional repletion.

16. Ischemic tissue injury. R. B. Jennings, C. E. Ganote, and K. A. Reimer. Am. J. Path. 81: 179-194, 1975.

Because of the morbidity and mortality of ischemic disease in Western societies, the functional defects caused by ischemia, as well as the pathogenesis of lethal ischemic cellular injury, have been studied by many investigators trained in several basic disciplines. This diversity has sometimes resulted in imprecision of terminology and misinterpretation of the relationships between the overall physiologic state initiating ischemia and the local cellular and subcellular changes which result. Thus, our aim in this paper is to define ischemia, illustrate local variations in the severity of the ischemic process, and review the functional and structural changes which develop during the acute phase of severe ischemic injury in the myocardium.

The subendocardial to subepicardial gradient in the severity of ischemia following acute coronary occlusion is described. The effects of mild, moderate, and severe ischemia on cell structure and function are compared in summary form, and special attention is given to the effects of severe ischemia on myocardial cells. The characteristics of reversible and irreversible ischemic injury are defined in biologic terms. The failure of cell volume regulation in cells which have entered an irreversible state of ischemic injury is demonstrated by the use of free-hand slices in vitro. Irreversibility is associated with structural defects in the plasma membrane and is reflected in an increased slice inulin-diffusible space, increased slice H_2O and Na^+ content, and failure of the tissue to maintain the high K^+ and MG^{2+} levels characteristic of normal left ventricular myocardium. Defective cell membrane function is an early feature of irreversible ischemic injury and may be a primary event in the genesis of the irreversible state.

17. Coronary perfusion and myocardial metabolism during open-heart surgery in man. B.G. Barratt-Boyes, E.A. Harris, A.M. Kenyon, C.A. Lindop, and E.R. Seelye. J. Thor. Cardiovasc. Surg. 72: 133-141, 1976.

There is as yet no concensus about the conditions of artificial coronary perfusion necessary to provide optimal survival of the myocardium during open-heart surgery. In particular, the optimal coronary perfusion pressure and flow during aortic valve replacement in hearts with left ventricular hypertrophy are conjectural.

Myocardial oxygen consumption and extraction of lactate and free fatty acids (FFA) have been measured in 6 patients during cardiopulmonary bypass at two coronary flow rates differing by 25% (109 and 148 ml/min). Significant differences were found between these flows and between natural and artificial coronary perfusion. This fact indicates the presence of anaerobic metabolism, especially at the lower coronary flow. These findings are discussed in relation to criteria for coronary flow and perfusion pressure during open-heart procedures.

18. Intravenous glucose-tolerance, insulin, and free-fatty-acid levels in burned patients. S. P. Allison, P. Hinton, and M. J. Chamberlain. Lancet 2: 1113-1116, 1968.

Intravenous glucose-tolerance tests performed during the shock phase of burn injury, and repeated 1-4 weeks later, show that in the shock phase there is glucose intolerance, a high level of free fatty acids, and failure of the plasma-immunoreactive-insulin level to rise in response to intravenous glucose. These changes have been shown to be related to the severity of the burn; they may be due to the high level of adrenaline secretion found in such patients. In the later phase there were higher than normal blood-levels of fasting insulin and of insulin response to glucose, suggesting insulin resistance. It is suggested that burned patients should be put on a high-carbohydrate regimen, which, in view of these results, should be in the form either of glucose and insulin or of fructose.

19. Association of lactoferrin with lysozyme in granules of human polymorphonuclear leukocytes. M. S. Leffell and J. K. Spitznagel. Infect. Immun. 6: 761-765, 1972.

Lactoferrin is contained in cytoplasmic granules of human polymorphonuclear leukocytes. Upon centrifugation, it sediments in a band of granules that also contain 50% of the lysozyme activity. This granules class is distinct from others associated with alkaline phosphatase and peroxidase. The granules are latent for lactoferrin as only lysed granules have the capacity specifically to inhibit antigen binding by anti-lactoferrin serum.

20. Direct measurement of insulin secretory rate: Studies in shocked primates and postoperative patients. J. M. Hiebert, J. M. McCormick, and R. H. Egdahl. Ann. Surg. 176: 296-304, 1972.

(1) A new method for the measurement of insulin secretory rate has been described and applied to studies of monkeys in hemorrhagic shock and postoperative patients before and after glucose administration. This method is based on the measurement of portal blood flow and the portal-arterial concentration gradient.

(2) Hemorrhagic shock in monkeys leads to a significant decrease in insulin secretory rate due to both a decrease in insulin secretory rate due to both a decrease in portal blood flow and a narrowing of the portal-arterial insulin concentration gradient.

(3) Insulin secretory rate has been measured in post-operative patients and an early and late peak response have been demonstrated following glucose administration.

(4) Our data show that assessment of pancreatic beta cell function on the basis of peripheral and portal concentrations of insulin may be misleading, especially in states of significantly altered portal blood flow.

21. The nature of irreversible shock: Experimental and clinical observations. R. C. Lillehei, J. K. Longerbeam, J. H. Bloch, and W. G. Manax. Ann. Surg. 160: 682-710, 1964.

When patients in shock respond temporarily or not at all to blood, plasma or plasma substitutes, they are thought to be in irreversible shock. Our studies in the dog indicate that whether shock is induced by hemorrhage, bacterial endotoxins, epinephrine, or myocardial failure, there is a final common hemodynamic disturbance in the peripheral vascular bed. This disturbance is characterized at first by ischemic anoxia in which both the precapillary arterial sphincters (resistance vessels) and post-capillary venular sphincters (capacitance vessels) are tightly constricted, thus allowing little blood to enter the splanchnic bed. This is the period of reversible shock and lasts about 2-3 hours in the dog, regardless of the original insult. Within 4-5 hours, irreversible shock supervenes and is characterized by stagnant anoxia in which the precapillary arterial sphincters have lost their tone while the postcapillary sphincters are still constricted. Now blood can get into the splanchnic bed but exits with difficulty, and hydrostatic capillary pressure increases. As a result, plasma begins to leave the vascular system at the venous end of the capillaries and circulating blood volume is progressively decreased. As shock is further prolonged, the capillary beds lose their integrity and slough, allowing whole blood to sequester outside of, as well as inside, the vascular system. During this period, myocardial function, which already is suffering from decreased venous return, is even more severely depressed by the acidosis attendant on the peripheral circulatory stagnation. It is clear now why fluids added at this time are of only temporary benefit, for what is needed in addition to fluid replacement is some means of correcting the imbalance between the arterial and venular sphincters to prevent further stagnation. In numerous animal experiments, we have found that the combination of the adrenergic blocking agent phenoxybenzamine (Dibenzyline), 1 mg/kg intravenously, and plasma or low-molecular-weight dextran is an effective means for salvaging dogs from irreversible shock induced by various methods. Hydrocortisone when given intravenously in doses of 50 mg/kg acts also as an adrenergic blocking agent and restores normal relationships in the capillary bed even more effectively than Dibenzyline. The volume of plasma or dextran given, over and above replacement of known losses, often exceeds 25 ml/kg and is determined solely by the central venous pressure rather than by the blood volume. This is because measurements of blood volume in shock do not accurately reflect effective circulating volume. The adequacy of the circulating blood volume is best judged by observations of changes in central venous pressure. The effectiveness of this therapy is assessed by its influence on cardiac output, organ blood flow, selective and total peripheral resistance, central venous pressure, catecholamines, acid-base balance and renal function, as well as upon survival of the animal.

With this background as our guide, we are now treating patients suffering shock from trauma, infection, myocardial failure or combinations of these insults, with a regimen including pharmacologic doses of hydrocortisone or phenoxybenzamine in combination with blood, plasma, or dextran. The salutary results in these patients give added support to our belief that shock in man and animals is similar. This is not to say that all aspects

of shock are identical, for we know that the visceral organs which suffer the ravages of shock may vary among the species. Rather, these findings support our concept that the basis for irreversible shock resides in a disturbed peripheral circulation and we should make use of this knowledge to improve our results in treating patients.

22. The intestinal factor in irreversible endotoxin shock. R. C. Lillehei and L. D. MacLean. Ann. Surg. 148: 513-525, 1958.

Plasma loss, hematocrit increase, plasma hemoglobin increase, and hemorrhagic necrosis of the bowel, all of which characterize irreversible shock due to endotoxin, apparently result from sympathomimetic action of endotoxin on the bowel. Agents which have an adrenergic blocking effect prevent these deleterious effects of endotoxin and prevent death while the vasopressor drugs which are commonly used to treat this type of shock either are without effect or else actually potentiate the shock caused by endotoxin by increasing intestinal ischemia.

23. The effect of pitressin on cardiac output and coronary, hepatic, and intestinal blood flow. T. Drapanas, C. P. Crowe, W. K. T. Shim, and W. G. Schenk, Jr. Surg. Gynec. Obstet. 113: 484-489, 1961.

(1) The effect of slow intravenous infusion of pitressin on cardiac output, hepatic blood flow, and mesenteric blood flow was studied in anesthetized dogs.

(2) Pitressin produced a marked depression of portal vein and hepatic arterial blood flow during the infusion and for as long as 1 hr after its termination, and an average depression of total hepatic blood flow to 51% of control values resulted. Intestinal blood flow, measured through the superior mesenteric artery, was similarly depressed.

(3) Despite a transient increase in systemic arterial blood pressure, a marked reduction in cardiac output to an average of 58% of the control values was noted, lasting from 45 to 60 minutes after pitressin injection.

(4) Coronary blood flow dropped precipitously after small injections of pitressin coinciding with the appearance of brachycardia and cardiac arrhythmias including heart block.

(5) These experiments lend strong support to the hypothesis that pitressin produces a generalized vasoconstrictive effect throughout the body resulting in parallel reductions in cardiac output, coronary blood flow, and hepatic and intestinal blood flow.

(6) When pitressin was injected into normal, anesthetized dogs it did not appear to produce a selective or preferential redistribution of blood flow away from the splanchnic system.

24. Studies with radioactive endotoxin. III. The effect of tolerance on the distribution of radioactivity after intravenous injection of Escherichia coli endotoxin labeled with Cr^{51}. F. J. Carey, A. I. Braude, and M. Zalesky. J. Clin. Invest. 37 (Suppl. II): 441-457, 1958.

Although normal and tolerant animals both cleared sublethal doses of endotoxin rapidly and at approximately equal rates, a great difference was observed between tolerant and nontolerant animals in the hepatic localization and plasma clearance of massive doses of endotoxin. In tolerant animals massive doses of radioactive endotoxin were removed much more rapidly from the circulating blood and more of it was deposited in the liver and leukocytes than in the nontolerant animal. If circulating antibody (precipitin) was present in high titer, the endotoxin was removed from the circulation still more rapidly because of an enormous and instantaneous deposition in the lung. In mice this pulmonary deposition was only transient; but in rabbits the high pulmonary localization lasted for several hours.

These results indicate that tolerance to lethal doses of endotoxin depends on speedy and permanent removal of circulating endotoxin into hepatic and other cells. Although not essential for tolerance, circulating antibody may contribute to it by inducing rapid but temporary pulmonary removal which by itself cannot provide protection.

25. Phagocytosis: The department of defense. T. P. Stossel. New Eng. J. Med. 286: 776-777, 1972.

In the combat against pyogenic infection, the polymorphonuclear leukocytes constitute the first line of defense. They rapidly enter inflammatory foci, whereas the monocytes arrive at a slower pace and then differentiate into macrophages. Thus, the monocytes and the mononuclear phagocytes that line the viscera, are a second line of defense. Phagocytosis is the essence of both lines of this defensive system, and the overall manner in which it functions can be divided into seven stages. In the first, the bone marrow produces and mobilizes phagocytes in prodigious numbers. Secondly, bacterial products or inflammatory mediators interact with serum factors, including complement, to attract phagocytes into injured or invaded areas by chemotaxis. Thirdly, factors in normal serum, particularly gamma globulin and the third component of complement, opsonize microbes, rendering them tasty to the phagocytes. Fourthly, the phagocyte ingests opsonized microorganisms, encasing them within phagocytic vesicles. Fifthly, cytoplasmic structures that contain hydrolytic enzymes fuse with the phagocytic vesicles, secrete their coutents therein, and disappear, a process called degranulation. Sixthly, at the same time, the phagocytes generate hydrogen peroxide, the most important antimicrobial agent within the phagocytic vesicles. Therefore peroxidation is the major determinant leading, finally, to microbial killing.

This categorization provides a framework for analyzing "susceptibility to infection." Malfunction of mobilization, chemotaxis, opsonization, ingestion, degranulation, peroxidation or killing, singly or in concert, usually predisposes the host to an unusual quantity of pyogenic infections. In general, derangement of a particular step produces a characteristic clinical picture, and whether one or both lines of defense are affected dictates its severity.

26. Chronic tissue insulin resistance following hemorrhagic shock. N. T. Ryan, B. C. George, D. H. Egdahl, and R. H. Egdahl. Ann. Surg. 180: 402-407, 1974.

Major trauma or shock are commonly associated with glucose intolerance, resistance to administered insulin, and excessive urinary nitrogen loss, which is not reversed by provision of carbohydrate. These abnormalities usually persist for several days after injury, even though often accompanied by elevated circulating insulin levels. This report describes an investigation of tissue glucose and amino acid metabolism as influenced by insulin following hemorrhagic shock with reinfusion. The data show a defect in tissue insulin sensitivity, with corresponding impairment of insulin regulated metabolism, which persists for at least one week after re-establishment of normal blood volume and pressure.

Metabolism of fat and muscle tissue was measured for 30 days following shock and reinfusion in rabbits. Tissue insulin resistance in the post-shock period was demonstrated by decreased oxidation of glucose and decreased incorporation of glucose into neutral lipid or glycogen during incubation with insulin. In addition, the insulin stimulated incorporation of amino acids into muscle protein was markedly reduced after shock. Conversely, the capacity of muscle to oxidize leucine was enhanced by shock, even in the presence of insulin. Tissue insulin resistance and increased leucine catabolism are likely to contribute to the general metabolic response to shock and trauma.

27. Treatment of diabetic coma with small intravenous insulin boluses. N. Clumeck, A. de Troyer, R. Naeiie, G. Somers, L. Smekens, and E. O. Balasse. Brit. Med. J. 2: 394-396, 1976.

The clinical efficacy of small intravenous boluses of insulin in treating diabetic decompensation was tested in 23 patients presenting in either a ketoacidotic or a nonketotic diabetic coma. In addition to the usual ionic and fluid replacement, the patients received hourly intravenous injections of insulin 5 IU. This dose lowered blood glucose levels in all but two patients. In the patients who responded the percentage decrease in glycaemia was similar whatever the initial glucose concentration and averaged ($\pm$SE of mean) 50$\pm$3% in 5 hours. Close monitoring of insulin and glucose concentrations after intravenous insulin in three patients showed that despite the short half life of insulin the effect of the intravenous bolus lasted for about 60 minutes. The overall clinical effectiveness of this type of treatment is comparable to that of the other low-dose regiments. Owing to its simplicity, this technique of insulin administration seems most suitable for the routine treatment of diabetic coma.

28. The neutrophilic leukocyte in wound repair. A study with antineutrophil serum. D. M. Simpson and R. Ross. J. Clin. Invest. 51: 2009-2023, 1972.

The role of the neutrophilic leukocyte in wound healing was investigated by observing the progress of repair in the absence of these cells. Circulating neutrophils were eliminated in guinea pigs by the administration of antineutrophil serum (ANS) 24 hr before wounding and by daily injections throughout a 10-day period of healing. Control animals received normal rabbit serum at the same dose levels and times. The wounds consisted of six linear incisions in the dorsal skin of the animals.

The contents of 24-hr neutropenic and control wounds were compared by quantitating the major cellular and extracellular wound components using a histometric technique. At 24 hr, there were no differences between control and neutropenic wounds in the per cent of total wound volume occupied by mononuclear leukocytes and fibrin. The neutropenic wounds had no neutrophils, had a significantly decreased volume of fluid space, and an increased volume of red cells, as compared with controls. The differences in numbers of erythrocytes and amount of fluid space in these two sets of wounds may be related to substances within neutrophils that promote lysis of erythrocytes or affect vascular permeability.

In spite of the lack of neutrophils in the ANS-treated animals during the 10 days of healing, no differences were observed between the control and neutropenic wounds relative to the rate of wound debridement or the extent of repair. The wounds from the two groups of animals were identical in cellularity and degree of connective tissue formation.

These observations support the notion that neither wound debridement nor the formation of granulation tissue are dependent upon the presence of neutrophils. A neutrophil response in early wounds is not an essential antecedent to the infiltration of monocytes, as suggested by previous investigations.

29. The role of the macrophage in wound repair. A study with hydrocortisone and antimacrophage serum. S. J. Leibovich and R. Ross. Am. J. Path. 78: 71-89, 1975.

The role of the monocyte macrophage in wound repair has been investigated by studying the healing process in wounds depleted of this cell and/or its phagocytic activity. Hydrocortisone acetate (0.6 mg g body weight) administered as a subcutaneous depot was used to induce a prolonged monocytopenia in guinea pigs, and antimacrophage serum (AMS) was used for local elimination of tissue macrophages. In vitro, in the presence of complement, macrophages are rapidly lysed and killed by AMS. In the absence of complement, AMS is not cytotoxic but potentially inhibits adherence to and phagocytosis of opsonized erythrocytes by macrophages. AMS titers were obtained by observation of adherence and phagocytosis of opsonized erythrocytes in serial dilutions of AMS. Six groups of animals were studied: a) untreated animals, b) animals receiving daily subcutaneous injections of normal rabbit serum (NRS) around each wound, c) animals receiving daily subcutaneous AMS around each wound, d) animals receiving systemic hydrocortisone, 3) animals receiving systemic hydrocortisone and daily injections of NRS around each wound, and f) animals receiving systemic hydrocortisone and daily AMS around each wound. Wounds consisted of a series of six linear incisions in the dorsal skin. Subcutaneous AMS alone had no effect on the number of circulating monocytes, nor was there any observable effect on the number or the phagocytic ability of wound macrophages. Fibrosis in these wounds was unaffected. Systemic hydrocortisone induced a prolonged monocytopenia. The macrophage level in the wounds of these monocytopenic animals was reduced to approximately one-third that of controls; the phagocytic activity of the monocytes macrophages that did appear in these wounds was, however, similar to that of controls. Some inhibition of wound debridement was observed in these wounds, but fibrosis was virtually unaffected. Collagen synthesis, as judged morphometrically, was similar to that of control wounds at all stages of repair. Conjoint systemic hydrocortisone and subcutaneous AMS around each wound resulted in the almost

complete disappearance of macrophages from the wounds. Wound fibrin levels were elevated, and clearance of fibrin, neutrophils, erythrocytes and other miscellaneous debris from these wounds was delayed. Fibroblasts, which in control wounds first appear by 3 days postwounding and reach maximal levels by day 5, did not appear in these wounds until day 5, and their subsequent rate of proliferation was slower than that of controls. Seven and 10 day wounds appeared immature both in terms of the degree of debridement, and extent of fibrosis. These studies indicate that in the repair process, the principle cell type responsible for wound debridement is the macrophage. In addition, the macrophage may be required to stimulate fibroblast proliferation in some as yet unidentified manner.

30. Depressed neutrophil chemotaxis in patients with chronic renal failure and after renal transplantation. D. J. Salant, A.-M. Glover, R. Anderson, A. M. Meyers, R. Rabkin, J. A. Myburgh, and A. R. Rabson. J. Lab. Clin. Med. 88: 536-545, 1976.

Bacterial infections are a major cause of morbidity and mortality in patients with renal failure. Acute infections are frequently encountered in patients who have undergone renal transplantation and to a lesser extent in those on dialysis. Although depressed cell-mediated immunity and an impaired antibody response have been demonstrated in uremia, polymorphonuclear leukocyte (PMN) function has not been fully elucidated.

This study was designed to assess chemotaxis, phagocytosis, and bactericidal ability of PMN's from patients with chronic renal failure treated conservatively or by dialysis or subsequent to transplantation. In addition, the ability of endotoxin-activated serum from these patients to generate chemotactic factors was studied.

Polymorphonuclear leukocyte chemotaxis, phagocytosis, and bactericidal ability were tested with neutrophils from patients with chronic renal failure on conservative therapy, from others on regular peritoneal dialysis or hemodialysis, and from a group of patients who had received renal allografts. Chemotaxis was depressed in all groups. Phagocytosis was mildly impaired in the two groups on dialysis. The leukocytes of patients on conservative therapy had mildly decreased killing ability, whereas this function was normal in other groups tested. Sera from all patients, when activated with endotoxin, were poorly chemotactic to normal neutrophils, especially in those on conservative therapy and hemodialysis, but these sera functioned normally as opsonins for phagocytosis. The observed defect in chemotaxis could account, at least partly, for the frequency of bacterial infections in these patients.

31. Sodium nitroprusside: Pharmacology, toxicology and therapeutics. J. H. Tinker and J. D. Michenfelder. Anesthesiology 45: 340-354, 1976.

Sodium nitroprusside is a potent, effective, and readily reversible direct vasodilating agent. It is broken down by hemoglobin into cyanide, which is in part detoxified by liver and kidney to thiocyanate. Some cyanide, especially in nitroprusside-"resistant" individuals who need large amounts of the drug, appears to remain free to cause cyanide poisoning. Patients requiring inordinate amounts probably should not continue to receive the drug, although maximum dosage limits for long-term therapy are not established. Blood thiocyanate levels do not indicate the extent to which free cyanide is limiting oxygen utilization in essential tissue, nor do blood cyanide levels. Metabolic acidosis, elevated lactate levels,

elevated lactate/pyruvate ratios, and elevated mixed venous blood oxygen content are at present the best indications of the presence of cyanide poisoning during nitroprusside administration.

Nitroprusside appears useful for induction of hypotension during surgery, and for treatment of hypertensive emergencies from all causes, although continuance for more than a few days is probably unwise. The reductions of cardiac afterload and ventricular filling pressure by nitroprusside appear useful in treatment of severe myocardial failure or infarctoin, but studies of myocardial cyanide toxicity are needed before complete acceptance of this therapy is warranted. Initial dose rates between 0.5 and 1.5 µg/kg/min are recommended only as starting points for very careful titration. Total projected intraoperative dosage should be calculated as quickly as possible and should not exceed 3-3.5 mg/kg. It is hoped that future studies will reveal the maximum dose of nitroprusside that can safely be metabolized in a 24-hour period, and may indicate that cofactors or rhodanase such as thiosulfate, or cobalamins such as hydroxocobalamin, can be administered with nitroprusside to prevent cyanide poisoning.

32. Myocardial oxygen availability and cardiac failure in hemorrhagic shock. J. C. Lee and S. E. Downing. Am. Heart J. 92: 201-209, 1976.

The relationships between left ventricular function and myocardial O_2 availability and metabolism were studied in cats with hemorrhagic shock (AP=30 mmHg) with the use of a right heart bypass preparation. Aortic flow and heart rate were held constant. Oxygen-carrying capacity was reduced by diluting donor blood with an equal volume of 5% glucose in saline. Oxygen availability was estimated as the product of arterial O_2 content and coronary blood flow. All shock animals showed a progressive metabolic acidemia with time, and a fall in coronary flow concomitantly. Four control animals (AP=75 mmHg) as well as two shock animals with high arterial oxygen content and hematocrit showed no significant changes in myocardial O_2 metabolism or performance over a period of 90 min. Nine shock animals with reduced hematocrit demonstrated a progressive reduction in ventricular function, myocardial O_2 metabolism, and O_2 availability. As O_2 availability fell below 10 ml/min/100 gm of heart weight, cardiac failure uniformly appeared and was accompanied by a reduction in O_2 extraction and consumption. The correlation between left ventricular dP/dt max and O_2 availability was highly significant ($r=0.75$, $p<0.01$) in shock animals but not in controls. Thus a close relationship between myocardial O_2 metabolism and function during the course of hemorrhagic shock has been demonstrated. Reduced myocardial O_2 availability is directly linked with the appearance of cardiac failure.

33. Studies of the absorption and metabolism of glucose following injury. The systemic response to injury. J. M. Howard. Ann. Surg. 141: 321-326, 1955.

As a manifestation of the metabolic response to injury, the oral glucose tolerance curve becomes diabetic in type and the insulin tolerance curve demonstrates a flattening in its pattern. Both the decreased glucose tolerance and the resistance to insulin appear proportional to the degree of injury. Both abnormalities diminish as convalescence progresses. One study suggests that the resistance to insulin persists longer in the face of severe infection.

Following injuries of several types, the battle casualty was found to absorb an appreciable amount of glucose from the gastrointestinal tract as indicated by striking elevations in the blood sugar concentration. Under conditions of mass casualties many such patients may, as a compromise, have to receive water and solutions orally. Further quantitative studies are essential to determine the limitations of this form of therapy.

34. Decline in pancreatic insulin release during hemorrhagic shock in the baboon. G. S. Moss, G. Cerchio, D. C. Siegel, P. C. Reed, A. Cochin, and V. Fresquez. Ann. Surg. 175: 210-213, 1972.

A study was carried out to determine if the previously described fall in peripheral insulin during hemorrhagic shock in baboons reflects a fall in pancreatic insulin release. Five adult baboons, with chronically implanted portal vein catheters, were subjected to 2 hrs of hemorrhagic hypotension (mean arterial pressure 60 mmHg). Paired portal and caval insulin measurements demonstrated a decline in both portal and caval insulin levels during the entire shock period, and a significant correlation between caval and portal insulin levels during shock.

It is concluded that hemorrhage produces inhibition of pancreatic release of insulin, and that a fall in peripheral insulin levels reflects a diminished pancreatic insulin release.

35. Serum insulin response in hemorrhagic shock in baboons. G. S. Moss, G. M. Cerchio, D. C. Siegel, P. A. Popovich, and E. Butler. Surgery 68: 34-39, 1970.

Nineteen tranquilized baboons were subjected to hemorrhagic hypotension at 60 mmHg for one hour and 40 mmHg for a second hour. The general effects of shock included hemodilution and marked metabolic acidosis. Significant hyperglycemia was noted shortly after the onset of hemorrhage and persisted throughout the hemorrhage period. Despite the hyperglycemia, serum immunoreactive insulin levels (IRI) were found to be significantly reduced below base-line values during the first 30 min of the hemorrhage period. For the remainder of the shock interval, IRI levels were not significantly deviated from base line. These data suggest that an inhibition of insulin release may play a significant role in the production of hyperglycemia associated with hemorrhagic shock in primates.

36. Insulin response during hypovolemic shock. W. E. Bauer, S. N. M. Vigas, R. E. Haist, and W. R. Drucker. Surgery 66: 80-88, 1969.

Well-fed mongrel dogs subjected to hemorrhagic shock and maintained at a mean arterial blood pressure of 30 mmHg by removal or addition of blood as necessary demonstrated that the characteristic rise in blood glucose in early hemorrhagic shock is associated with a significant rise in plasma insulin. As shock continues the levels of both insulin and glucose decline. An infusion of glucose after prolonged hypovolemia, when metabolic and physiologic functions of the organism have started to deteriorate, elicits another rise in plasma insulin. These findings suggest that the hormonal mechanisms for energy metabolism are preserved after prolonged shock, though the adequate normal response to these hormonal changes may be prevented by circulatory effects.

37. Pancreatic blood flow and insulin output in severe hemorrhage. T. S. Lau, W. Taubenfligel, R. Levene, G. Farago, H. Chan, I. Koven, and W. R. Drucker. J. Trauma 12: 880-884, 1972.

(1) The pancreatic output of insulin during severe hemorrhage has been measured by a new surgical technique of isolation of a segment of the pancreas.

(2) There was a pronounced and abrupt output of insulin from the pancreas with hypogolemia when there was minimal hyperglycemia.

(3) The initial pronounced output of insulin from the pancreas rapidly declined even when blood glucose level continued to rise.

(4) There was sharp reduction of pancreatic blood flow throughout the period of study. This reduction was proportional to the fall in the cardiac output.

38. Experimental studies on coagulation-fibrinolytic activity of white blood cells influenced by endotoxin. N. Sakuragawa, K. Takahashi, M. Yoshiyama, C. Jimbo, K. Niiya, M. Matsuoka and Y. Ohnishi. Thromb. Res. 8: 887-891, 1976.

For the treatment of malignant diseases and leukemia, many drugs, for instance, adrenocortical steroids, 6-mercaptopurine and anti-inflammatory drugs, are used. These have inhibitory effects on the immunological mechanisms and function of white blood cells. Severe infection is complicated in these cases. Disseminated intravascular coagulation syndrome (DIC) is often observed in such cases with endotoxin shock. In this paper, we discuss the effects of endotoxin on the coagulation-fibrinolytic activities of white blood cells by in vitro and in vivo studies.

When infection occurs, white blood cells gather at the site of infection. These cells contribute coagulation-fibrinolytic factors and can serve as a trigger substance to evoke DIC in leukemia. We tried to find out how much influence endotoxin will have on the coagulation-fibrinolytic system of white blood cells.

39. Studies on plasma insulin levels in the posttraumatic phase in rabbits. J. P. N. Chansouria, A. K. Singh, K. N. Udupa. J. Trauma 13: 1063-1065, 1973.

We have reported changes in the plasma insulin and blood sugar levels in rabbits following fracture of the right femur. Significant increase in plasma insulin was noticed after 48 hr. Blood sugar levels also increased and remained high up to 72 hr. Elevated plasma insulin levels observed in the present study could be due to a generalized increase in the activity of islets of Langerhans, as seen in other endocrine glands in response to trauma.

40. Insulin resistance in experimental shock. I. H. Chaudry, M. M. Sayeed, and A. E. Baue. Arch. Surg. 109: 412-415, 1974.

Previously adrenalectomized (ADX) rats were bled to a mean arterial pressure of 40 mmHg and maintained for 1 1/2 hours. Basal glucose uptake by isolated soleus muscle from ADX normal rats and ADX rats subjected to

shock ("shock" muscles) increased with the increase in medium glucose concentration and uptake was similar in both groups of muscles. This indicates that shock per se did not produce any alterations in the basal glucose carrier mechanism. Insulin (0.1 unit/ml) increased uptake in ADX control but not in ADX shock muscles. Maximal stimulation of glucose uptake in shock muscles was observed at an insulin concentration of 0.2 unit/ml insulin. These experiments provide the first direct evidence that the responsiveness of tissues to insulin is altered during shock. This alteration could not be due to increased steroid or epinephrine output during shock.

41. Effect of surgical Pituitrin upon portal and hepatic circulation. I. Heimburger, S. Teramoto, and H. B. Shumacker, Jr. Surgery 48: 706-715, 1960.

Portal venous pressure, portal venous oxygen saturation, portal blood flow, and total hepatic blood flow have been studied in anesthetized dogs given single or repeated injections of surgical Pituitrin and in dogs given a continuous infusion of Pituitrin. Following a single injection of surgical Pituitrin a prompt, marked, but transient decrease in portal flow occurs. A similarly prompt, marked, but somewhat more sustained decrease in portal pressure is noted. The saturation of the portal venous blood falls. Hepatic blood flow decreases somewhat less than portal blood flow and the response is even more brief. Similar responses are observed repetitively when repeated injections of Pituitrin are given. With the continuous infusion of Pituitrin, portal blood flow drops to a low level and is maintained. A similarly sustained decrease in portal pressure is noted. Hepatic blood flow falls immediately but soon afterward rises to a level within 30% of the normal value. A negligible increase in arterial blood pressure accompanies the infusion of Pituitrin. The difference in the response of the portal and of the hepatic blood flow to the infusion of Pituitrin is interpreted on the basis of the contribution of hepatic arterial inflow into the liver. These observations suggest that during the infusion, hepatic vascular resistance decreases with a concomitant increase in hepatic arterial inflow.

The experimental observations suggest the desirability of continued exploration of the potential usefulness of infusions of Pituitrin in the management of patients with bleeding esophageal varices.

42. Effects of sodium pentobarbital anesthesia on left ventricular function and distribution of cardiac output in dogs, with particular reference to the mechanism for tachycardia. W. T. Manders and S. F. Vatner. Circ. Res. 39: 512-517, 1976.

Sodium pentobarbital remains one of the most widely used anesthetics for experimental cardiovascular studies. However, the effects of the anesthetic agent are generally disregarded in the interpretation of experimental data from studies in which PB is employed. This is due in part to the fact that the effects of this anesthetic are not completely known. In addition, results from previous studies, which indicated that the anesthetic has little effect on cardiac output and arterial pressure, have previously been used as justification for disregarding its effects.

The primary goal of this study was to provide a comprehensive picture of the effects of sodium pentobarbital (PB) on left ventricular (LV) function, coronary dynamics, distribution of regional blood flow, and regional vascular resistance. A secondary goal was to examine the mechanism for the PB-induced tachycardia, which is currently thought to be due to a vagolytic action.

Sodium pentobarbital (PB), 30 mg/kg, iv, was administered to 30 conscious dogs instrumented for measurement of cardiac output and regional blood flow distribution, left ventricular (LV) diameter, LV pressure, dP/dt, and dD/dt, i.e., velocity of myocardial fiber shortening. Ventilation was controlled during anesthesia to maintain arterial blood gases at control values for conscious dogs. The anesthetic produced an initial transient peripheral vasodilation but the steady state effects 15-30 min later were characterized by slight reductions in mesenteric flow and cardiac output and increases in mesenteric and systemic resistances, whereas iliac and renal resistances were not significantly different from control. When heart rate rose, PB increased end-systolic diameter and decreased coronary resistance, LV end-diastolic diameter, dP/dt/P (42%), and shortening velocity (36%). When heart rate was controlled, PB still increased end-systolic diameter and decreased shortening velocity and dP/dt/P, as occurred during spontaneous rhythm, but end-diastolic diameter rose instead of falling and coronary resistance did not change. After recovery from bilateral cervical section of both carotid sinus and aortic nerves, PB failed to elicit tachycardia. Thus, PB affects sytemic and regional hemodynamics only slightly, but depresses the myocardium markedly. The tachycardia associated with PB anesthesia in intact, trained dogs appears not be only vagolytic, as previously thought, but is predominantly mediated through the arterial baroreceptor reflex.

43. 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.

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.

44. Effects of sodium nitroprusside and nitroglycerin on tension prolongation of cat papillary muscle during recovery from hypoxia. B. R. Brodie, L. Chuck, S. Klausner, W. Grossman, and W. Parmley. Circ. Res. 39: 596-601, 1976.

Vasodilators have become widely used in the treatment of left ventricular failure complicating acute myocardial infarction, mitral regurgitation, and primary myocardial disease. There has been a number of studies concerning the effects of vasodilators on systolic performance but little is known about their effects on diastolic properties of the left ventricle. Recent studies in man indicate that vasodilators are capable of altering the left ventricular diastolic pressure-volume relationship so that, for a given volume, the pressure is lower during vasodilator administration. One possible explanation for this finding is that vasodilators may exert a direct relaxant effect on ventricular muscle similar to their known relaxant effect on vascular smooth muscle. The present study was designed to explore this possibility and examine the effects of sodium nitroprusside and nitroglycerin on parameters of myocardial relaxation in isolated cat papillary muscle preparations. The results indicate that nitroprusside is capable of blocking the tension prolongation that occurs during recovery from hypoxia but that nitroglycerin has no effect on tension prolongation.

Because of recent studies suggesting that vasodilators affect ventricular compliance, we studied the effect of sodium nitroprusside and nitroglycerin on the mechanical performance of 21 isolated cat papillary muscles. The muscles were stimulated isometrically at 36 beats/min. Sixteen of the muscles were made hypoxic (95% N_2, 5% CO_2) for 50 min and then reoxygenated. Sodium nitroprusside (10^{-5} M added to four of these muscles prior to hypoxia substantially diminished the tension prolongation (both the time to peak tension, TTP, and the time for tension to fall to 1/2 its peak value, $RT_{1/2}$), that characterizes recovery from hypoxia. TTP and $RT_{1/2}$ measured 2 min after reoxygenation were 300±20 msec and 528±26 msec for the control muscles compared to 208±13 msec and 248±22 msec for the muscles pretreated with nitroprusside. Nitroprusside had no effect on the fall and recovery of peak developed force or on the rise and fall of resting force. Furthermore, nitroprusside had no effect on the above parameters in nonhypoxic muscles. We also found that nitroprusside in concentrations of 10^{-5}M and nitroglycerin in concentrations of 10^{-5}M had little or no effect on tension prolongation. The results of the study indicate that nitroprusside is capable of blocking the tension prolongation that occurs during recovery from hypoxia and may prevent the incomplete myocardial relaxation thought to characterize this phenomenon. Since nitroglycerin had no effect on tension prolongation, it is possible that other factors also may be important in the apparent increase in left ventricular compliance associated with administration of vasodilators to patients.

45. Perturbation by bacterial lipopolysaccharide of the metabolic process of human cells in continuous culture. S. G. Bradley and D. B. Howe. J. Reticuloendo. Soc. 20: 135-145, 1976.

Relatively few workers have observed direct cytotoxicity of endotoxin from gram-negative bacteria. Woods et al. have reported that endotoxin stimulated cellular glycolysis when added to a suspension of melanoma cells. The stimulatory action of endotoxin on glycolysis was enhanced

by increasing the serum concentration in the incubation medium. Mesrobeanu et al. reported that endotoxin was cytotoxic for cultures from normal adult or embryonic tissue but was not cytotoxic for cells of tumor origin. Similarly Vaheri et al. reported that nanogram amounts of bacterial endotoxin caused increased sugar uptake, increased thymidine incorporation and increased cell number in density-inhibited cultures of chick embryo fibroblasts. Kessel et al. observed morphologic damage to cultured macrophages after treatment with endotoxin but they concluded that an endotoxin-specific Ab was involved. Endotoxin has been reported to alter the susceptibility of cultured cells to other agents; for example, endotoxin accelerated the cytopathogenic action of poliovirus. Other effects of endotoxin at the cellular level include changes in migration of macrophages and platelet damage. However, the search for a cellular basis for the mechanism of action of bacterial endotoxin has not been successful in providing a means to probe the molecular action of endotoxin.

The ability of bacterial lipopolysaccharide (LPS) to perturb the metabolic processes of human embryonic lung (WI-38) cells in continuous culture has been assessed. Lipopolysaccharide (Escherichia coli 0127:B8, Boivin preparation) alone did not alter the uptake of Adenine, Leucine, Serine, Thymidine or Uridine by WI-38 cells but did alter the distribution of these radiolabeled metabolites among the cellular macromolecules. Moreover, the uptake of Adenine and Leucine was markedly retarded by a combination of cycloheximide and LPS. Similarly, the uptake of Serine was markedly retarded by a combination of mithramycin and LPS. A combination of vincristine and LPS markedly retarded uptake of Adenine, Leucine, Serine and Uridine. LPS elicited comparable changes whether serum was present or absent in the culture medium. Bacterial LPS consistently altered the metabolism of WI-38 cells and rendered them more susceptible to the alkaloid vincristine.

46. Ultrastructural damage of leukocytes procured by the Leukopak: Vulnerability of leukocytes to mechanical injury. C. Ts'ao and E. A. Ruder. Transfusion 16: 336-344, 1976.

Because of the often observed undesired effects in patients transfused with leukocytes collected by continuous filtration leukapheresis (CFL), we have investigated the morphology of these cells in the hope that such studies may help evaluate their in vivo functions. Aliquots of CFL samples, procured by the Fenwal Leukopak and taken before and after tapping the filters, were examined. Leukocytes prepared by dextran sedimentation served as controls and were used to demonstrate the vulnerability of these cells to mechanical injury. The morphology of leukocytes harvested by filtration leukapheresis was markedly altered, ranging from formation of cytoplasmic projections and vacuoles to disintegration of entire cells. The severe changes were only observed in samples collected after the filters were tapped. The number of cells involved varied from donor to donor. In some cases more than half of the examined leukocytes showed signs of damage. Dextran sedimentation leukocytes retained their normal ultrastructure. However, substantial injuries were inflicted on dextran sedimentation collected leukocytes following brief periods of vortexing. Our results indicate that leukocytes are quite vulnerable to mechanical injury, and the major cause of damage found in Leukopak-isolated leukocytes is the tapping of the filters. The toxic reactions in some recipients transfused with Leukopak-collected leukocyte preparations may result from materials released from disrupted leukocytes. We believe that the employment of the continuous filtration to procure leukocytes with the present procedure should be reviewed.

47. Defective neutrophil function in chronic granulocytic leukaemia. H. El-Maalem and J. Fletcher. Brit. J. Haematol. 34: 95-103, 1976.

The ability of neutrophils to phagocytose, kill and digest Candida guilliermondii was investigated in 12 patients with chronic granulocytic leukaemia (CGL). Following ingestion of organisms there was considerable reduction in the ability of CGL cells to kill Candida and this was not explained by a mild impairment of phagocytosis. Histochemical staining showed that granules containing lysosomal enzymes disappear from the cytoplasm of normal neutrophils during killing and digestion of the fungus, while in CGL cells the granules remain. Quantitative measurement confirmed loss of peroxidase from normal neutrophils during Candida killing but no loss from CGL neutrophils. The primary granules of CGL neutrophils do not fuse with and discharge their contents into the phagocytic vacuole and this explains their impaired ability to kill and digest Candida.

48. Immunological impairment and susceptibility to infection after splenectomy. V. V. Likhite. J.A.M.A. 236: 1376-1377, 1976.

Although its function in humans is poorly understood, the spleen is involved mainly in the clearance of particulate antigens as well as injured or old cells within the host. Altered RBCs are cleared much less rapidly in splenectomized individuals. They also exhibit siderotic granules and nuclear remnants in cells released prematirely by the marrow, which would normally have been pitted by the spleen. Asplenic persons also show changes in RBC, leukocyte, and platelet morphology, along with leukocytosis and thrombocytosis. Studies performed on animals and man demonstrate that the spleen has several functions, namely: (1) the clearance of particulate antigens, (2) the elaboration of specific immune responses, and (3) the production of opsonins.

Asplenic patients or those who have undergone splenectomy are prone to overwhelming and often fatal sepsis, which is sometimes associated with disseminated intravascular coagulopathies. Although several pathogens are involved, the most common organism found in these subjects is the pneumococcus, and the infections respond poorly to antibiotic therapy.

49. Granulocyte function and pseudomonas burn wound infection. D. D. McEuen, G. C. Gerber, P. Blair, and K. Eurenius. Infect. Immun. 14: 399-402, 1976.

Infection with Pseudomonas aeruginosa remains the major cause of death in burn patients. Attempts to eliminate such infection with the use of topical antibacterial therapy and systemic antibiotics have been only minimally effective and point to the necessity of a better understanding of the burn patient's host defense. Although alterations in humoral immune defense mechanisms have been cited, the experimental and clinical use of immune vaccines and passive immunization with pseudomonas antibody have not altered mortality in this disease state. Impaired granulocyte function, granulocytopenia, and altered serum opsonic activity have all been implicated as crucial defects in host defense in the presence of a pseudomonas infection.

Granulocyte function in burn injury has been evaluated with an in vitro animal assay. Bactericidal activity, using this technique, was markedly depressed only when granulocytes from scald burned rats were challenged with each of three strains of Pseudomonas aueroginosa in the presence of autologous postburn serum or heat-inactivated serum. Preincubation of postburn and normal serum at 37°C for 1 hr resulted in normal phagocytosis. These studies

validate an investigation of plasma and/or granulocyte replacement therapy in the burned patient.

50. Progressive perfusion impairment during prolonged low flow myocardial ischemia in dogs. L. H. Frame and W. J. Powell, Jr. Circ. Res. 39: 269-276, 1976.

Recent studies have shown that after total coronary artery occlusion, there is impaired "reflow" of blood accompanied by myocardial and capillary endothelial cell swelling. To investigate the effect of prolonged low flow myocardial ischemia on coronary vascular resistance, regional hypoperfusion of the distal left anterior descending coronary artery was studied in 31 autonomically blocked dogs on right heart bypass. Heart rate, aortic pressure, and, during ischemia, left ventricular end-diastolic pressure were held constant. The distal left anterior descending coronary artery was perfused at a substantially reduced perfusion pressure which resulted in an antegrade coronary blood flow that usually was between 3% and 7% (0.5-1 ml/min) of control. When relative hypothermia (33-34°C) was induced in nine dogs, left anterior descending coronary artery vascular resistance did not change during 2.5-3 hours of low flow ischemia. Under euthermic conditions (37-40°C) in 19 dogs there was a consistent progressive increase in distal left anterior descending coronary artery vascular resistance starting at 90 min (median) after onset of ischemia. By 110-140 min ischemic antegrade flow decreased by 35±4% (SEM) ($p<0.01$). Directionally similar flow changes were observed in six euthermic experiments using the krypton-85 washout technique. Light microscopy did not reveal hemorrhage as a cause of the increased vascular resistance. The perfusion impairment did not occur in two euthermic, nonischemic hearts. In five dogs elevation of serum osmolality by 23±11 mOsmol/liter with mannitol attenuated the progressive decrease in flow. Thus, a progressive perfusion defect exists in the ischemic low flow state in the heart which presumably contributes to the extent of eventual necrosis.

51. Growth of the concept of shock and review of present knowledge. R. C. Lillehei, R. H. Dietzman, G. J. Motsay, C. B. Beckman, L. H. Romero, and C. H. Shatney. In: Steroids and Shock, edited by T. M. Glenn. Univ. Park Press, 1974, pp. 377-413.

The usual causes of shock occurring during and following operative surgery are associated with a decrease in effective circulating blood volume, which may be due to external blood as in trauma, or pooling within the circulation, or both, as commonly occurs in gram-negative septic shock or congestive failure with cardiac damage. All these conditions elicit a viscerocutaneous vasoconstrictive response mediated through baroreceptors. The later stages of this response are characterized by stagnation in the microcirculation of the viscera and skin with loss of tone in arterioles, and venous outflow obstruction due to venular constriction or aggregation or both, or microthrombi within the stagnant circulation. The problems resulting from such a process include a decrease in the effective circulating blood volume, which may represent an actual loss of blood volume or pooling of large volumes within the circulation, and a disturbance in the microcirculation. Effective treatment must include restoration of effective circulating blood volume, which usually means the administration of additional fluids and the correction of the microcirculatory disturbance. The most effective, safe, available agents to do this, presently available, are glucocorticosteroids, given in

massive doses. The usual dosage has been 30 mg/kg of methylprednisolone, given as an intravenous bolus. Inotropic agents, such as levarterenol, meteraminol, and isoproterenol, are occasionally used for their inotropic or chronotropic effects, but only after methylprednisolone is given. In this situation we have found that these inotropic agents become more effective in smaller doses and have less toxicity. A protocol utilizing this plan of treatment has resulted in an over-all survival of more than 70% of patients suffering traumatic, septic, or cardiogenic shock or combinations of these problems.

52. Endotoxins and leukocyte mobilization. G. J. Fruhman. J. Reticuloendo. Soc. 12: 62-79, 1972.

Mice respond to a single intraperitoneal injection of a bacterial endotoxin by: (1) a marked depletion of mature neutrophils from the bone marrow, (2) an immediate decrease in the numbers of circulating neutrophils, and (3) a delayed pattern of neutrophil mobilization into the peritoneal fluid. When such mice are challenged 10 days later by a second injection of the same endotoxin, marrow depletion of mature neutrophils is less marked, circulating neutrophils are less severely depressed, and neutrophil mobilization is improved.

Improved neutrophil mobilization into the peritoneal fluid is most marked when pretreatment and challenge are done with the same endotoxin. Pretreatment and challenge with different endotoxins results in only a small improvement in the neutrophil response. These results are consistent with the idea that the formation of immune complexes in challenged animals reduces the toxicity of the endotoxin and also increases the formation of chemotactic substances in the area of inflammation.

53. Leukotactic responses. P. A. Ward. J. Reticuloendo. Soc. 19: 247-248, 1976.

Leukotactic responses are currently measured most commonly by the use of micropore filters in modified Boyden chambers. Quantitative problems in assessing migration of leukocytes have been diminished by the use of radiotagged leukocytes which are trapped in the interstices of a second filter (1). Another modification of quantitative approaches is the "leading front" technique in which the depth of penetration of migrating cells is the parameter measured. Neither of these 2 modifications has yet replaced the conventional morphologic approach. The structural basis of chemotactic activity is under considerable study. There are some suggestions that tertiary structural changes in peptides or proteins, resulting in the exposure of hydrophobic regions, account for the acquisition of chemotactic activity. However, on the basis of studies with synthetic peptides, there is firm chemical evidence that the primary structure is a critical factor in chemotactically active compounds.

Several biochemical parameters reflect interaction of a chemotactic factor with the leukocyte: increased oxygen uptake by the cell, glycolysis, activation of the hexose monophosphate shunt and activation of a proesterase. Additional concomitant changes include lysosomal enzyme discharge and assembly of microtubles.

The sources of leukotactic factors include plasma proteins and cells. The former category includes the complement proteins (related to the third, C3,

and the fifth, C5, components), kallikrein and the plasminogen activator. The latter category includes, by and large, cell-released enzymes that can cleave C3 or C5, and newly formed products released after cell or tissue activation following contact with antigen. The products released from cells consist of the preformed eosinophil chemotactic factor and newly synthesized proteins such as the monocyte chemotactic factor released from stimulated lymphoid cells.

Regulation of the leukotactic system occurs by the action of 2 different inhibitors found in human serum: the chemotactic factor inactivator (CFI) and the cell directed inhibitor (CDI). Chemotactic factor inactivator reacts irreversibly with leukotactic factors, is present in low concentrations in human serum and exists in two forms in serum: an α globulin which has specificity for the C5 fragment and a β globulin which interacts specifically with the C3 leukotactic fragment. In addition to reactivity with leukotactic factors, CFI also inactivates the migration inhibitory factor produced by lymphoid cells. Current studies indicate that CFI has the enzymatic activity of an amino peptidase. Cell directed inhibitor is cell directed in its action and blocks the ability of both neutrophils and monocytes to respond to a variety of leukotactic stimuli. Cell directed inhibitor also impairs the phagocytic responses of neutrophils. When plasma/serum levels of either CFI or CDI are elevated, there are evidences of impairment of the inflammatory response.

54. High-dose glucose-insulin-potassium in treatment of irreversible hemorrhagic shock. R. H. Whitten and R. H. Egdahl. Surg. Forum 27: 60-62, 1976.

Previous studies have demonstrated glycogen depletion, glucose intolerance, tissue insulin resistance, and inappropriately low endogenous insulin production following hemorrhagic shock. It is unclear whether these alterations contribute to mortality. Glucose infusions have been shown to improve cardiac outputs in hypotensive combat casualties better than equiosmolar infusions of saline or mannitol. Insulin and glucose were significantly more effective than glucose alone in prolonging short-term survival of rabbits in deep hemorrhagic shock. This study was designed to determine if high-dose glucose, insulin, and potassium (GIK) can significantly increase long-term survival of rabbits following resuscitation from profound hemorrhagic shock.

High-dose GIK is effective in significantly increasing long-term survival of rabbits following resuscitation from profound hemorrhagic shock. It is uncertain whether this observed benefit is derived from direct inotropic action on the myocardium, increased extracellular osmolarity, intracellular transport of potassium and phosphate, provision of energy substrate, reduction of free fatty acid mobilization, direct augmentation of protein anabolism, or other known actions of glucose, insulin, and potassium.

55. Responsiveness of isolated dog veins to bradykinin and other bioactive peptides: Distribution of sensitivity to bradykinin and possible correlation with genesis of the venous system. H. Tsuru, N. Ishikawa, and T. Shigei. Blood Vessels 13: 238-248, 1976.

Contractile responses of isolated dog veins to bradykinin were studied. Responses to norepinephrine were taken as standards. According to their sensitivity to bradykinin, the veins obtained from 14 sites of the venous system were divided into two groups, while all the veins were almost uniform in their sensitivity to norepinephrine. One group has high sensitivity to bradykinin and the other has low sensitivity. The former includes the pulmonary, hepatic, splenic, and portal veins, the anterior vena cava, and

the upper and the middle divisions of the posterior vena cava. The latter includes the external jugular, cephalic, azygos, femoral, and saphenous veins, and the lower division of the posterior vena cava. The responses of the renal vein were intermediate. A striking correlation was noted between the distribution of bradykinin sensitivity and the genesis of the venous system.

Five bioactive peptides other than bradykinin were also studied. Only angiotensin induced contraction in some preparation, but, as a whole, caerulein, eledoisin-related peptide, oxytocin and vasopressin rarely showed contractile activity.

56. Effects of anoxia and glucose depletion on isolated veins of the dog. P. M. Vanhoutte. Am. J. Physiol. 230: 1261-1268, 1976.

Canine vein strips were mounted for isometric tension recording. Anoxia did not affect basal tension of saphenous and pulmonary strips mounted in standard Krebs-Ringer solution or after 30 min of incubation in glucose-free solution. Anoxia depressed the strength of spontaneous contractions of mesenteric veins; in glucose-free solution (30 min), anoxia relaxed the strips. Veins placed in glucose-free solution for more than 60 min contracted with anoxia; this contraction was not inhibited by iproveratril. When the vein strips were contracted by norepinephrine or KCl, anoxia depressed the contractions, most in mesenteric and least in saphenous preparations; this depression was greater in the absence of glucose. When oxygen was present, the absence of glucose had little effect on the response to vasoactive agents. Contractions with acetylcholine were depressed by anoxia in mesenteric and pulmonary strips but were augmented in saphenous vins; the latter potentiation was inhibited by iproveratril and by incubation in glucose-free solution. Thus, especially in the saphenous vein, anaerobic glycolysis can provide most of the energy requirements, and intracellular substrates are available for oxidative metabolism.

57. Normal carbohydrate metabolism and carbohydrate metabolism in trauma. E. Hultman, J. Bergstrom, and L. H:son Nilsson. Acta Anaesth. Scand. 55: 28-49, 1974.

The great lability of man's glucose reserves as shown by the decreases in liver glycogen both during short starvation, decreased intake of carbohydrate or as an effect of trauma shows the importance of carbohydrate administration both in the normal man and in the treatment of trauma. Even if a relative intolerance to glucose is seen in the post-traumatic phase, it seems reasonable to use glucose possibly together with insulin as the basic caloric supply. The most important reason for this is that during hypoxia, which can readily occur, the only useful fuel is glucose transported via the blood or stored in the tissues as glycogen.

58. Effects of cardiopulmonary bypass on the phagocytic and bactericidal capacities of polymorphonuclear leukocytes. E. L. Kaplan, A. R. Castaneda, E. M. Ayoub, and P. G. Quie. Supplement II to Circulation 37 & 38: 158-167, 1968.

Studies on phagocytosis, intracellular digestion, and bactericidal capacity of polymorphonuclear leukocytes from patients undergoing cardiac surgery requiring a pump oxygenator reveal no significant abnormalities in these separate and distinct events. Furthermore, these cells reveal no differences from normal polymorphonuclear leukocytes in the morphological changes

following phagocytosis. Polymorphonuclear leukocytes from heparinized fresh blood used for transfusions also demonstrated normal function. It is doubtful if impaired function of polymorphonuclear leukocytes from these patients contributes significantly to their apparently increased susceptibility to bacterial infection.

59. Experimental endotoxin shock. The effect of hypothermia on outcome. T. B. Williams and D. Cavanagh. Am. J. Obstet. Gynecol. 108: 1171-1174, 1970.

The potential value of hypothermia in reducing the oxygen demand of tissues during endotoxin shock is evident and so its use in canine endotoxin shock was investigated. An extracorporeal technique of inducing hypothermia is described as applied to three groups of dogs and the results are given. All animals receiving only hypothermia (Group A) survived. In animals receiving endotoxin alone (Group B) there were no survivors. In animals receiving endotoxin and hypothermia (Group C), the hypotension was less profound than that observed in the Group B animals, but only one animal survived over 36 hours. Despite the theoretical advantages of hypothermia it appeared to have no significant effect on the outcome.

60. Effect of pitressin on the splanchnic circulation in man. S. Shaldon, W. Dolle, L. Guevara, F. L. Iber, and S. Sherlock. Circulation 24: 797-807, 1961.

The effects of 20 units of pitressin administered intravenously on the splanchnic circulation in four patients without liver disease, 10 patients with cirrhosis and a patent portal vein, 11 patients with cirrhosis and an end-to-side portacaval anastomosis and two patients with an extrahepatic portal vein obstruction and a normal liver structure, were observed. Estimated hepatic blood flow and wedged hepatic venous and intrasplenic pressures were measured in all groups, and the splanchnic, hepatic arteriolar, and hepatic postsinusoidal resistances were calculated. Pitressin reduced the portal pressure by an average of 39% for 1 hour. Estimated hepatic blood flow was reduced by 40%. Splanchnic resistance was increased by 87% and hepatic arteriolar resistance by 77%. Postsinusoidal resistance was not affected. The drop in portal pressure could be related to the increases in splanchnic resistance. There was no difference in the response to pitressin between patients with cirrhosis and patients with normal liver structure and function. It is suggested that the fundamental lesion causing portal hypertension in cirrhosis is an obstruction to the hepatic venous outflow is not alterable pharmacologically and any attempts to lower portal pressure by medical means must be achieved by alterations in the splanchnic resistance. Pitressin appears to be the most potent splanchnic vasoconstrictor available.

61. Effect of hypertonic glucose in hypovolemic shock in man. J. J. McNamara, M. D. Molot, R. A. Dunn, and J. F. Stremple. Ann. Surg. 176: 247-250, 1972.

Combat casualties in hypovolemic shock were resuscitated in the usual fashion and, at the same time received, by random selection either nothing else or equal osmolar doses of 50% glucose, 25% mannitol or 3% saline. Glucose produced an increase in blood pressure and pulse pressure which was significantly greater and of longer duration than any of the other groups. The mechanism by which this occurs and importance in resuscitation is discussed.

62. Insulin: Fundamental mechanism of action and the heart. R. J. Kones and J. H. Phillips. Cardiology 60: 280-303, 1975.

Insulin accelerates the entry of glucose and amino acids into muscle cells by acting upon the 'carrier-facilitated' transport mechanism. For glucose this process is passive and leads to equilibration of intracellular and extracellular concentrations. In heart muscle, glucose transport is a rate-limiting step for glucose uptake. During hypoxia and ischemia the heart turns to anaerobic glycolysis for energy production and therefore, maximal glucose transport becomes important. Insulin is necessary to insure proper protein synthesis, probably at the level of membrane-bound polyribosomes. However, during myocardial hypoxia, insulin alone cannot restore the associated depression in protein synthesis. Although insulin hyperpolarizes the cell, a change in the ratio of intracellular to extracellular activities of potassium is not its primary mode of action. An insulin-induced configurational change in the plasma membrane could simultaneously account for the effects of insulin on sodium and potassium permeability and the action on facilitated transport. Intracellular levels of cyclic adenylate may be reduced by insulin in adipose tissue because of inhibition of adenyl cyclase or stimulation of phosphodiesterase. However, at this time there is little evidence that insulin alters cyclic AMP levels in the heart. Insulin secretion is depressed in patients with heart disease in proportion to the reduction of cardiac index sustained. Since the ischemic heart is dependent upon glucose as the major fuel, insulin lack may deprive the heart of adequate substrate.

63. Afterload-induced homeometric autoregulation in isolated cardiac muscle. T. C. Donald, D. M. Peterson, A. A. Walker, and L. L. Hefner. Am. J. Physiol. 231: 545-550, 1976. •

Pressure-induced homeometric autoregulation (HAR) has been demonstrated by many investigators in the mammalian ventricle. In isolated cardiac muscle, however, several investigators have reported the opposite effect (anti-HAR); namely, that the first beat after a transition from isotonic to isometric contraction is the most forceful, with a decline over several beats to a steady state. In the present study we find that trabeculae from the canine right ventricle demonstrate either HAR or anti-HAR, depending on the rate of stimulation, the calcium level, and the temperature. Higher calcium, higher temperature, and lower rate of stimulation produce either less HAR or more anti-HAR. When only temperature and rate of stimulation are varied, in each muscle there is a unique rate for each temperature above which HAR occurs and below which anti-HAR occurs.

64. Bioassay of endotoxin clearance in vivo and by perfused rat liver. B. J. Buchanan and J. P. Filkins. Am. J. Physiol. 231: 258-264, 1976.

Endotoxin clearances in vivo and by the isolated perfused rat liver were evaluated via bioassay in lead-sensitized rats. A linear relationship between the probit of shock lethality and the endotoxin dose in the probit range of 4-6 was validated. Endotoxin clearance in normal, fed rats displayed a linear relationship between the logarithm of the blood endotoxin concentration and time throughout the period of 15-240 min at doses of 500 and 1,000 μg/rat; the half-time values were 58-63 min. Decreasing the endotoxin dose to 250 μg resulted in multiphasic clearance curves. Induction of tolerance to endotoxin resulted in marked acceleration of endotoxin clearance. Endotoxin clearance from the isolated perfused rat liver was not influenced by serum or rat blood as compared to clearance from a balanced

salt solution. These data suggest that a physiologically stressful dose of endotoxin is slowly cleared from the blood and, therefore, circulates for prolonged periods.

65. Hypoglycemic depression of RES function. B. J. Buchanan and J. P. Filkins. Am. J. Physiol. 231: 265-269, 1976.

The intravascular removal rates of colloidal carbon and of biologically active endotoxin by the reticuloendothelial system (RES) were evaluated as a function of blood-glucose levels. There was a significant negative correlation of carbon clearance half time on blood glucose in both saline-treated and insulin-treated rats. Insulin hypoglycemia depressed RES carbon clearance with the maximal effect occurring at blood glucose values below 30 mg/dl. Insulin hypoglycemia also severely impaired the intravascular removal of endotoxin as evaluated by lethality bioassay in lead-sensitized rats. It is concluded that blood glucose may modulate RES phagocytic function and that the hypoglycemia of endotoxin shock may augment the shock state due to impairment of RES host defense clearance functions.

66. Beneficial effect of prostaglandin E_1 in experimental hemorrhagic shock. G. W. Machiedo, C. S. Brown, J. E. Lavigne, and B. F. Rush, Jr. Surg. Gynec. Obstet. 143: 433-436, 1976.

Twelve dogs were subjected to hemorrhagic shock by means of a modified Wiggers technique. Half were treated with prostaglandin E_1, 1 µg/kg/min in 60 ml of saline solution, for one hour after shock, while the other half received only an equal amount of saline solution. Those dogs treated with prostaglandin E_1 exhibited a significantly increased survival time and cardiac output as well as a significantly lowered total peripheral resistance when compared with those for untreated dogs. The various modes of action by which prostaglandin E_1 exerts both its cardiovascular and other long term effects indicate a multisystem effect of the drug.

67. Myocardial reperfusion, a cause of ischemic injury during cardiopulmonary bypass. R. M. Engelman, R. Chandra, F. G. Baumann, and R. A. Goldman. Surgery 80: 266-276, 1976.

Reperfusion following myocardial ischemia has been postulated to cause myocardial edema resulting in increasing interstitial pressure and retardation of the microcirculation. If ischemia then is repeated, the additional insult results in increasing edema and possible infarction. In order to test this hypothesis, 15 pigs were placed on cardiopulmonary bypass with coronary perfusion maintained at 100 mmHg by a separate pump through the clamped aortic root. Coronary flow and vascular resistance were recorded. Distribution of coronary blood flow was monitored by injection of radioactively labeled microspheres (15 µ). Myocardial extravascular water was measured by simultaneously determining myocardial intravascular water with radioactive iodinated serum albumin (RISA) and total myocardial water with tritiated water (THO). Three 30-min periods of myocardial ischemia and 5 min of coronary perfusion produced (1) a loss of the reactive hyperemic response to ischemia (coronary vascular resistance increased--from 0.295±0.024, control, to 0.366±0.042, after anoxia--rather than decreasing with reactive hyperemia induced vasodilatation); (2) a significant maldistribution of coronary flow away from the endocardium (endocardial: epicardial perfusion ratio 1.10±0.05, control, to 0.69±0.08, following ischemia, $p<0.05$); and (3) significant myocardial edema. Myocardial extravascular water rose from 46.4±1.7 ml/100 Gm

control, to 52.6±2.0 ml/100 gm, after ischemia ($p<0.05$), whereas intravascular myocardial volume did not change significantly. Both light and electron microscopic examination of the postischemic myocardium shows interstitial and intracellular edema with typical ischemic changes at a cellular and subcellular level. The significant increase in myocardial extravascular water content associated with this injury supports the concept that myocardial reperfusion plays a role in its development.

68. The properties and biologic effects of bacterial pyrogens. I. L. Bennett, Jr., and P. B. Beeson. Medicine 29: 365-400, 1950.

An attempt has been made to bring together the present knowledge of the properties and biologic effects of bacterial pyrogens. Evidence implicating them as the principal causes of febrile reactions to intravenous injection of biologic materials has been summarized. Pyrogenic substances are produced by many different kinds of bacteria. The most potent pyrogens are produced by gram-negative bacilli, especially members of the coliform, Salmonella and Pseudomonas groups. In these organisms pyrogenic activity seems to be closely associated with the somatic antigen.

The pyrogens which have been isolated chemically appear to be large polysaccharide molecules, which pass through porcelain filters, but are partially adsorbed by asbestos and charcoal. They are relatively resistant to heat and are able to withstand autoclaving. Pyrogens have been employed extensively in studies on temperature regulation and pathogenesis of fever. Evidence favors the hypothesis that their effect on temperature regulatory centers is an indirect one, secondary to tissue injury. Human beings and experimental animals are capable of developing a tolerance to the fever-producing and injurious effects of pyrogens. This tolerance is not related to the development of humoral antibodies, but may be due to an increased ability of the reticuloendothelial system to remove pyrogen from the circulation.

The principal histologic change caused by administration of large doses of pyrogens is widespread capillary damage. Under certain circumstances the area of damage is sharply localized, as in the Swartzman phenomenon and the hemorrhagic necrosis which is produced in certain tumors. Pyrogens have been investigated for possible value in the therapy of human neoplastic disease. It has not been demonstrated that any of the manifestations of bacterial infections are effects of pyrogenic substances produced by the bacteria. On the other hand there are a few occupational disorders in which exposure to bacterial pyrogens seems to be the essential factor. These include such syndromes as "cotton-fever" and "zinc fever", where the symptoms appear to be caused by absorption of pyrogens from the respiratory tract.

Injection of pyrogens is followed by striking changes in the circulating leukocytes: an immediate leukopenic reaction, followed later by a leukocytosis. Failure to recognize this appears to have led to numerous errors in interpretation of experimental results. Pyrogens also have a pronounced effect on hemodynamics. There is a lowering of blood pressure associated with increased renal blood flow. These changes have been studied for possible value in the treatment of hypertension.

Other pharmacologic effects of bacterial pyrogens include depression of gastric acid secretion and motility.

Numerous biochemical alterations have been noted following injection of bacterial pyrogens, the most striking being depletion of liver glycogen. Doubtless some of the effects of pyrogens on body chemistry and function are due to their effect in stimulating release of adrenal cortical hormone.

69. Phenoxybenzamine--a mediator of blood oxygen affinity. G. M. Watkins, T. D. Johnson, M. L. Wenk, and E. J. Lovett. J. Trauma 16: 566-572, 1976.

Laborit and Nickerson first introduced the concept of alpha blockade in the treatment of shock. Nickerson published initial observations concerning the clinical use of phenoxybenzamine. When infused immediately before or shortly after induction of shock, phenoxybenzamine has improved both microcirculation and metabolism. Increased survival in animals subjected to shock has been established. Studies also have indicated that phenoxybenzamine has membrane sparing effects. Data supporting the usefulness of phenoxybenzamine in clinical practice have become more difficult to interpret. Phenoxybenzamine has not been approved for clinical use, so that, in humans, other agents such as chlorpromazine and regitine have been employed for induction of alpha blockade.

Studies of the effect of phenoxybenzamine on oxygen tranport have been concentrated on flow and resistance changes. Previous studies have ignored the possible effects of phenoxybenzamine on the ability of red blood cells to offload oxygen itself. After an initial inhibitory effect phenoxybenzamine greatly enhances the ability of the red cell to offload oxygen under conditions seen at the tissue level. The disparity between P_{50} std and organic phosphate changes found in this and other studies warrants extreme caution to be used in interpreting results where P_{50} itself is not measured.

70. The left shifted oxyhemoglobin curve in the burn patient. A. G. Greenburg, H. Frank, and G. W. Peskin. J. Trauma 16: 573-578, 1976.

As in other forms of acute significant stress, a left shift of the oxyhemoglobin dissociation curve is noted in the thermally injured patient. This response, inappropriate to the observed pH, does not appear to be influenced by alterations in 2,3-DPG, osmolality or phosphate nor does it appear to influence cardiovascular dynamics. Analysis of the position of the curve may be useful in the prognosis of burn stress and evaluating appropriateness of therapy.

71. Nitroprusside after open-heart surgery. G. Benzing III, J. A. Helmsworth, J. T. Schrieber, J. Loggie, and S. Kaplan. Circulation 54: 467-471, 1976.

The effects of intravenous infusion of sodium nitroprusside were studied in 11 children immediately after open-heart surgery for congenital heart disease. The patients were selected because, following bypass, their cardiac index was below 2.0 $L/min/m^2$ and their systemic vascular resistance exceeded 30 units. In order to eliminate the effects of preload, mean left atrial pressure was maintained at a constant level by blood transfusion. During infusion of nitroprusside the mean decrease of mean arterial pressure was 18.6%, of systemic vascular resistance was 53.7%, and the increase in cardiac index was 76.9%. All children recovered.

72. Why aspirin? (Editorial.) P. W. Majerus. Circulation 54: 357-359, 1976.

Recent interest in the use of aspirin as an agent for prevention of myocardial infarction has focused attention on the pharmacology of the drug. The rationale for the use of aspirin depends on the hypothesis that platelet aggregation and release have a role in the pathogenesis of myocardial infarction and/or atherosclerosis. The evidence for the hypothesis will not be presented here but it is certainly far from conclusive. Rather, I will present recent data which elucidates the role of prostaglandin synthesis in platelet physiology and the mechanism by which aspirin interferes with prostaglandin synthesis.

Topics discussed are as follows: (1) role of platelets in hemostasis; inhibition of platelet function by aspirin, and (2) role of prostaglandin synthesis in platelet reactions; inhibitory mechanism of aspirin on prostaglandin synthesis.

73. Steroids in the treatment of clinical septic shock. W. Schumer. Ann. Surg. 184: 333-341, 1976.

In a recent criticism of previous investigations with steroids, Weitzman and Berger stated, "Only future studies with sufficient adherence to sound principles of clinical trial design can resolve the controversy surrounding the use of corticosteroids as adjunctive therapy in bacterial infection." Therefore, this report presents a prospective and a retrospective study of our clinical experience with the use of steroids in septic shock. A prospective (Part I) and a retrospective (Part II) study were used to determine the safety and efficacy of corticosteroids in the treatment of septic shock. In Part I, 172 consecutive patients in septic shock admitted over an 8-year period were treated with either steroid or saline: 43 received dexamethasone (DMP), 43 received methylprednisolone (MPS), and 86 received saline. The study was double-blind and randomized, and the three groups were compared for age, severity of shock, presence of underlying disease, and year of study. In the 86 saline-treated patients, the mortality rate was 38.4% (33/86); in the steroid-treated patients, it was 10.4% (9/86). With MPS the mortality rate was 11.6% (5/43), and with DMP it was 9.3% (4/43). Thus, overall mortality was significantly less in the steroid-treated group than in the control groups. Further, there was no significant difference in mortality rate between the DMP- and MPS-treated patients. In Part II, 328 patients were studied retrospectively. One-hundred sixty were treated without steroid, and 168 were treated with either DMP or MPS. Again, the two groups of patients were compared for severity of shock, underlying disease, age, and year of study. Mortality among patients treated without steroid was 42.5% (68/160) and among patients treated with steroids was 14% (24/168); there was no significant difference in mortality rate between DMP- and MPS-treated patients. In Parts I and II combined, complications occurred in 6% of steroid-treated patients with no significant difference between DMP- and MPS-treated groups.

74. Wound healing. R. Ross. Scient. Amer. 220: 40-50, 1969.

When a salamander loses a leg, it can grow a new one, but man has not retained this ability to duplicate injured tissue. The liver and the surface layer of the skin are among the few mammalian tissues that can regenerate themselves; otherwise man must rely on wound healing. This is an intricate physiological process in which several different kinds of cells appear at

succesive intervals in order to absorb foreign matter, destroy bacteria and repair the injury.

Clearly wound repair is essential to health and comfort. It also represents a biological adaptation without which complex multicellular organisms could neither survive nor evolve. Because of its medical importance the general character of the process has been known for years. Recently, however, the advance of biochemistry and the development of the electron microscope and other research tools have enabled investigators to observe and understand in greater detail the molecular events that manifest themselves on the macroscopic level as inflammation, scar formation, restoration of the skin's surface and the other stages of wound repair. Furthermore, because the study of wound repair involves examining some of the most basic features of living tissue, progress in this field of inquiry could yield information that might lead to new understanding of such illnesses as cancer, rheumatoid arthritis and rheumatic heart disease.

75. Alanine metabolism and gluconeogenesis in the rat. M. MacDonald, N. Neufeldt, B. N. Park, M. Berger, and N. Ruderman. Am. J. Physiol. 231: 619-626, 1976.

The metabolism of alanine and several other gluconeogenic substrates was studied in anesthetized fed and fasted rats, i.e., rats with low and high rates of gluconeogenesis. Glutamine was released by the hindquarter (muscle) in both groups, whereas lactate, pyruvate, and alanine were taken up in fed rats and were released during starvation. Despite this, blood levels of alanine, lactate, and pyruvate were diminished in fasting rats, suggesting increased extraction by liver. Treatment of fasted rats for 24 hr with phloridzin caused glycosuria and secondarily led to hypoglycemia and an intensification of the charges observed with fasting, i.e., hyperketonemia, hyperglucagonemia, and increased gluconeogenesis (assessed by urea N excretion). Blood alanine was decreased, even though the release of alanine from muscle was increased. Pretreatment with triamcinolone and administration of exogenous alanine both attenuated the hypoglycemia and ketosis. It is concluded that (1) in states of heightened gluconeogenesis, alanine release from muscle may not keep pace with extraction by liver and blood alanine decreases; (2) the release of alanine, lactate, and pyruvate from muscle parallel each other suggesting common control factors; and (3) in the fed state muscle is an important site of lactate disposition.

76. Neutrophil kinetics in man. J. T. Dancey, K. A. Deubelbeiss, L. A. Harker, and C. A. Finch. J. Clin. Invest. 58: 705-715, 1976.

A method has been developed for measuring neutrophil cellularity in normal human bone marrow, in which the neutrophil-erythroid ratio was determined from marrow sections and marrow normoblasts were estimated by the erythron iron turnover. Neutrophil maturational categories, defined by morphologic criteria, were supported by autoradiographs of marrow flashed-labeled with ^{3}H-thymidine. Correction for multiple counting error was empirically derived by counting serial sections through cells of each maturational category. The normal neutrophil-erythroid ratio in 13 normal human subjects was 1.5±0.07. The mean number of normoblasts in the same subjects was estimated to be 5.07±0.84 X 10^{9} cells/kg. Total marrow neutrophils (X 10^{9} cells/kg) were 7.70±1.20, the postmitotic pool (metamyelocytes, bands, and segmented forms) was 5.59±0.90 and the mitotic pool (promyelocytes + myelocytes) was 2.11±0.36.

Marrow neutrophil ("total") production has been determined from the number of neutrophils comprising the postmitotic marrow pool divided by their transit time. Transit time was derived from the appearance in circulating neutrophils of injected ^{3}H-thymidine. The postmitotic pool comprised 5.59± 0.90 X 10^{9} neutrophils/kg, and the transit time was 6.60±0.03 days. From these data marrow neutrophil production was calculated to be 0.85 X 10^{9} cells/kg per day.

Effective production, measured as the turnover of circulating neutrophils labeled with ^{3}H-thymidine, was 0.87±0.13 X 10^{9} cells/kg per day. This value correlated well with the calculation of marrow neutrophil production. A larger turnover of 1.62±0.46 X 10^{9} cells/kg per day was obtained when diisopropylfluorophosphate-^{32}P was used to label circulating neutrophils. Studies using isologous cells doubly labeled with ^{3}H-thymidine and diisopropylfluorophosphate-^{32}P demonstrated a lower recovery and shorter $t_{1/2}$ of the ^{32}P label.

77. Effect of glucose-insulin-potassium infusions on arteriovenous differences of glucose and of free fatty acids and on tissue metabolic changes in dogs with developing myocardial infarction. L. H. Opie and P. Owen. Am. J. Cardiol. 38: 310-321, 1976.

Glucose-insulin-potassium infusions were given to dogs for 6 hours, starting 30 min after ligation of the left anterior descending coronary artery. Effects on substrate arteriovenous differences, indexes of ischemic damage and other tissue metabolic changes were compared with changes in dogs with comparable ligations but no infusions. Glucose-insulin-potassium increased the arteriovenous difference of glucose, decreased that of free fatty acid and decreased the arterial free fatty acid/albumin molar ratio. Glucose-insulin-potassium accelerated the rate of fall of the epicardial S-T segment in the infarct zone and prevented the small rise in S-T segment found in the periinfarct and nonischemic zones. Glucose-insulin-potassium increased the tissue content of glycogen in peripheral infarct, periinfarct and nonischemic zones; increased tissue potassium ion-sodium ion ratios in epicardial infarct zones and in the periinfarct zone; increased adenosine triphosphate in the endocardial infarct zone; decreased inorganic phosphate in the periinfarct and nonischemic zones and in the endocardial infarct zone; and increased lactate in the central infarct and nonischemic zones. The phosphate potential increased in the periinfarct and nonischemic zones. Thus, many glucose-insulin-potassium effects were greater in the peripheral infarct and especially the periinfarct zones. Although increased anaerobic metabolism with lactate production could not be excluded as a mode of action of glucose-insulin-potassium, estimated rates of anaerobic glycolysis were very low, suggesting that other effects such as increased aerobic glycolysis decreased extraction of free fatty acid by the heart, increased tissue glycogen or a "membrane" effect might be of major importance.

78. How to control the blood glucose level in the surgical diabetic patient. A. A. Rossini and J. W. Hare. Arch. Surg. 111: 945-949, 1976.

This report is a sequel to "Why control blood glucose levels?" (Arch. Surg. 111:229, 1976), which linked complications of diabetes mellitus to poor control. Hyperglycemia, increased gluconeogenesis, nitrogen wasting, and increased ketogenesis occur in the perioperative period, partly as a result of contrainsulin hormones provoked by stress and trauma. These untoward events are aggravated in the diabetic. Zones of levels of blood glucose

control are charted, as well as the corresponding insulin needs for each of these zones. Intermediate insulins should provide basic coverage; regular insulin is recommended only as a supplement. Several blood glucose determinations per day are necessary to maintain control. The hazards of dependence on urine testing and the "sliding scale" for control are among a number of caveats discussed.

79. Glycogen metabolism in inflammatory macrophages. P. W. Gudewicz and J. P. Filkins. J. Reticuloendo. Soc. 20: 147-157, 1976.

Glycogen metabolism within mononuclear phagocytes was investigated in vitro utilizing rat peritoneal inflammatory macrophages harvested 96 hr after an i.p. injection of 1% sodium caseinate. The inflammatory macrophage was observed to contain a large glycogen content of 110.3±12.8 μg of glycogen per mg of protein. Studies were undertaken to investigate the mechanisms by which macrophages acquire and maintain this large glycogen reserve from the inflammatory environment. Macrophages incubated in vitro with 10 mM glucose maintained their large glycogen content during a 60 min incubation interval. Moreover, the addition of 10 mg/ml of glycogen to a glucose-free medium also enabled inflammatory macrophages to maintain their intracellular glycogen pool. Macrophage glycogen synthesis and degradation mechanisms were demonstrated by determining the activity of glycogen phosphorylase, glycogen synthetase and also an α-glucosidase. Total macrophage phosphorylase was measured in the presence of adenosine-5'-monophosphate (5'-AMP) while macrophage active phosphorylase activity (73% of the total activity) was measured in the absence of 5'-AMP. Inflammatory macrophages also exhibited a large α-1, 4 glucosidase activity of 201±1.0 μg of glucose hydrolyzed per hr per mg of protein. Macrophage α-1, 4 glucosidase activity exhibited its greatest activity at pH 4.0, indicating that the enzyme was of probable lysosomal origin. Macrophage glycogen synthetase was found to exist in 2 forms, a dependent form requiring the presence of 10 mM glucose-6-phosphate and an independent form, manifesting 6% of the total activity in the absence of 10 mM glucose-6-phosphate. Thus, a large glycogen reserve within mononuclear phagocytes, involving regulatory synthetic and degradative pathways, provides the inflammatory macrophage with additional glucose to meet a wide spectrum of energy demands.

80. Neutrophil function in children with kwashiorkor. K. Schopfer and S. D. Douglas. J. Lab. Clin. Med. 88: 450-461, 1976.

Peripheral blood polymorphonuclear neutrophil (PMN) function has been investigated for 46 children with kwashiorkor (without overt infection) in the Ivory Coast, West Africa. In vitro chemotactic response, candidacidal activity, and kinetic studies of metabolism during phagocytosis have been performed. Postphagocytic morphological events were evaluated by electron microscopy. The reduction of nitroblue tetrazolium (NBT), measurement of enzyme activities, activity of glycolysis, and hexose monophosphate shunt (HMS) activity were assessed. The extent of iodide incorporation into trichloroacetic acid (TCA)-precipitable protein by phagocytizing PMN's and thyroid hormone degradation were measured. Chemotactic response was reduced at early time intervals (30, 60 and 120 min) and reached control values after 180 minutes. Whereas PMN's of controls killed 32.13±11.10% of Candida albicans after 60 min, PMN's from kwashiorkor patients killed 18.55±7.74% ($p<0.01$). HMS activity for resting PMN's of kwashiorkor children was higher than for controls, and during particle ingestion the extent of stimulation was comparable to controls. Electron microscopic assessment of phagocytic vacuole formation and degranulation showed no difference between PMN's

from kwashiorkor and control subjects. Incorporation of ^{131}I into TCA-precipitable proteins by phagocytizing PMN's from kwashiorkor children was reduced in comparison to controls, with either viable or heat-killed lactobacilli. No impairment in thyroxine (T4) degradation was observed for PMN's from kwashiorkor cases. PMN's from kwashiorkor patients show toxic granules, Döhle bodies, evidence of high baseline NBT reduction, and glucose decarboxylation. Functional studies indicate impaired kinetics of chemotaxis, diminished candidacidal activity, and reduced iodination. Enzymatic activities of resting cells are normal. Lactate production, HMS activity during phagocytosis, and morphological events are not impaired. Thus, impaired in vitro microbicidal activity, increased resting metabolism, and decreased iodination by PMN's may be related to the high incidence of infection in kwashiorkor.

81. Metabolic significance of skeletal muscle during normal and shock conditions. A. Arango, H. Illner, and G. T. Shires. Surg. Forum 27: 43-45, 1976.

The final pathway of the organism in shock is probably determined by the extent of the cellular injury. Since skeletal muscle represents 50% of the cellular mass of the body and is a tissue largely unprotected during shock, a proper understanding of the metabolic and functional alterations of the muscle tissue is important in the overall evaluation of the shock state. The aim of the present study was to document the role of skeletal muscle in the production and clearance of metabolic by-products during normal and shock conditions.

In the present study, mechanical perfusion of normal skeletal muscle resulted in perfusate changes similar to those found in the blood of animals in early hemorrhagic shock. This finding suggests a partial arrest of glycolysis at the anaerobic phase, probably secondary to a relatively poor perfusion. However, if the muscle is perfused under the same circumstances, but with blood from donors in shock, with high concentration of metabolites of anaerobic glycolysis, the muscle cell will actively clear these substances from the perfusate, implying the utilization of aerobic pathways despite the probable inadequate perfusion. On the other hand, after a prolonged period of shock, the muscle cell loses the ability to compensate perfusate abnormalities and continues to increase metabolic derangements contributing to a faster deterioration.

82. Endogenous fuels in experimental shock. A. M. Daniel, H. M. Shizgal, and L. D. MacLean. Surg. Forum 27: 32-33, 1976.

It has been shown that dogs in shock, regardless of its etiology, produced a higher percentage of CO_2 from substrates which form pyruvate and lactate as intermediates than do normotensive dogs. This finding implicated increased oxidation of carbohydrates and/or proteins and decreased oxidation of fatty acids in shock. To determine the relative importance of these three major endogenous fuels in shock, the turnover and oxidation rates of free fatty acids (FFA) and glucose, the production rate of urea, the disappearance rate of muscle glycogen, as well as oxygen utilization and carbon dioxide production were measured in shocked and control dogs.

Shock was established, either by controlled cardiac tamponade of by i.v. injection of Escherichia coli endotoxin, in dogs that had undergone 20-hr fast, had been anesthetized, and were breathing spontaneously.

The percentage of the total CO_2 production derived from FFA oxidation decreased more than eightfold in the shocked groups. This decrease in fatty acid oxidation was not compensated by increased blood glucose utilization. Both the turnover and oxidation rate of glucose remained normal in shock. However, the shocked animal used more of its stored carbohydrates, indicating a lesser dependence on gluconeogenesis to maintain normal glucose turnover. Livers of the control dogs contained about 10 mg/gm glycogen at the time of killing; the shocked dogs' livers had no glycogen left. Muscle glycogen loss was greater in the shocked dogs. The difference, however, was not significant statistically.

Urea production increased in shock from 9.0±3.9 in the normal to 14.9±1.0 μmoles/min/kg in dogs in shock ($p<0.001$). Calculating with a carbon: nitrogen ratio of 4:1 in amino acids, the possible maximum amount of CO_2 production from protein oxidation was found to be 23% in the control group and 51% in the shocked animals. Therefore, in shock, FFA--normally the major and most abundant endogenous fuel--is utilized poorly, and the organism depends on protein breakdown and oxidation for the maintenance of its energy balance.

83. Effects of glucose and alanine on energy metabolism in hemorrhagic shock. R. F. Seelig and B. F. Rush, Jr. Surg. Forum 27: 34-36, 1976.

Hemorrhagic shock impairs the production and utilization of metabolic energy in experimental animals and man. As alanine is a major substrate involved in gluconeogenesis, we evaluated its effectiveness in supporting peripheral energy metabolism in the post-hemorrhagic shock period. The importance of alanine as a major source of glucose through the glucose-alanine cycle has been described. The infusion of alanine following hemorrhagic shock appears not only to maintain hepatic glycogen levels but peripheral energy stores as well.

84. Improved survival in endotoxemia with aspirin and indomethacin pretreatment. J. R. Fletcher, C. M. Herman, and P. W. Ramwell. Surg. Forum 27: 11-12, 1976.

Pharmacological doses of nonsteroidal anti-inflammatory drugs (aspirin, indomethacin) decrease the acute hemodynamic responses during endotoxin shock and improve the survival rate. The mechanism by which these drugs exert their beneficial effects are unknown. We examined the possibility that they might act through suppression of prostaglandins with a resultant effect on survival, coagulation, complement, and hemodynamic changes in an LD_{50} endotoxin model.

(1) Acute (0-1 hr) pathological events appear to be important in death due to sepsis in this model. (2) Clinical doses of aspirin and indomethacin significantly improve the survival rate in septic shock in the dog. (3) Pretreatment with either aspirin or indomethacin prevents the rise in prostaglandins and improves the acute hemodynamic events when compared to nonpretreated groups. (4) Coagulation and complement changes are unrelated to prostaglandins and the presence of aspirin or indomethacin. (5) Prostaglandins are participants in septic shock of the dog, and it is unlikely that they mediate changes in the acute hemodynamic events by their effects on the coagulation and complement system.

85. Reversal of ischemically induced uncoupled oxidative phosphorylation by restoration of adequate perfusion. R. S. Rhodes and R. G. DePalma. Surg. Forum 27: 13-15, 1976.

Failure to produce high-energy phosphates (ATP) has been demonstrated in hepatic mitochondria during the late stages of Wigger's model of hemorrhagic shock. Since failure of circulatory homeostasis appears to occur concomitantly with mitochondrial failure, it has been difficult to restore adequate hepatic perfusion to determine whether the mitochondrial defect is also irreversible. Using an experimental model with induced ischemia of one hepatic lobe, we sought to reverse ischemically induced alterations of mitochondrial energy-linked functions by restoration of adequate tissue flow.

Various forms of experimental shock as well as hepatic ischemia have been demonstrated to impair hepatic mitochondrial energy-linked metabolism. Since the present model of hepatic ischemia can be controlled more precisely, it is possible to relate the effects of restoration of perfusion to recovery of certain mitochondrial functions.

The present study demonstrated that reversal of ischemically induced mitochondrial energy-linked dysfunction with restoration of perfusion appeared to be substrate dependent. The fact that neither lactate levels nor succinate-mediated state III respiration returned entirely to normal is consistent with the hypotheses that either the duration of reperfusion was insufficient or that irreversible damage may have occurred to at least a portion of the hepatic cell population.

86. Arteriovenous shunting in the canine hindlimb with sepsis. J. L. Cronenwett and S. M. Lindenauer. Surg. Forum 27: 24-26, 1976.

Septic shock with high cardiac output manifests a barrier to cell oxygenation which is poorly understood. The canine model used in this study, hindlimb with sepsis, demonstrates elevated mixed venous oxygen tension despite increased blood flow to infected tissue. This paper describes the correlation between these findings and the occurrence of peripheral arteriovenous (A-V) shunting.

Increased A-V shunting cannot be explained by local temperature change since both the infected and the normal contralateral leg increased in temperature equally. Furthermore, local foreign-body reaction without bacterial inoculation did not elevate A-V shunting more than in the contralateral leg, where only femoral dissection was performed. Although muscle capillary blood flow increased in the infected hindlimb, the amount of increase was not correlated with the increased femoral artery flow ($r=.05$). However, the 5-fold increase in A-V shunting correlated highly with increased femoral flow ($r=.95$, $p<.001$, linear regression). Furthermore, increased A-V shunting was correlated with decreased A-V O_2 difference ($r=.44$, $p<.02$). We conclude that increased A-V shunting contributes to the high blood flow but unchanged oxygen consumption demonstrated in the canine hindlimb with sepsis.

87. Alterations in adenosine 3',5'-monophosphate levels in hemorrhagic shock. I. H. Chaudry and A. E. Baue. Surg. Forum 27:51-53, 1976.

Previous work from our laboratory has shown that adenosine triphosphate (ATP) levels of various tissues decreased during shock and that alterations in membrane function occurred during shock. Since the formation of CAMP is through ATP, it seems reasonable to expect that this system might also be altered by blood loss. The present study was undertaken to determine the levels of CAMP in various tissues during shock, and our results indicate that there are significant decreases in tissue CAMP levels.

The results indicate that there are significant decreases in liver, kidney, muscle, and brain CAMP levels in shock. ATP levels in liver, kidney, and muscle also decrease significantly during shock. The decreases in CAMP levels follow the same trend in the various organs as the decreases in ATP levels, suggesting that these two events are related. The precise mechanism for decreased CAMP levels during shock is not known at present; however, it is possible that this is due to decreased ATP levels within the cell during shock. Further experiments are needed to determine if in vivo infusion of ATP increases the intracellular CAMP levels during shock.

88. Systemic and regional arteriovenous shunting in endotoxic and septic shock in dogs. J. P. Archie, Jr. Surg. Forum 27: 55-57, 1976.

The basic underlying defect in oxygen transport or metabolism in endotoxic and septic shock remains unclear. Anatomic arteriovenous shunting has been postulated as a possible mechanism of inadequate oxygen delivery in septic shock in man and experimental aniamls. Accordingly we measured systemic and regional anatomic arteriovenous shunting in two dog shock models.

The data show that systemic anatomic arteriovenous shunting is small and not different from control in both models. Regional arteriovenous shunting is increased in gut in the septic model and in kidney in the endotoxin model. Thus, significant anatomic arteriovenous shunting does not occur in these two dog models of endotoxic and septic shock. Other possible mechanisms of inadequate oxidative metabolism in endotoxic and septic shock are inadequate oxygen delivery because of physiologic shunting (impaired oxygen diffusion) and defects in oxygen utilization.

INDEX

UNCLASSIFIED
Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)	2a. REPORT SECURITY CLASSIFICATION
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER OKLAHOMA CITY, OKLAHOMA	UNCLASSIFIED
	2b. GROUP UNCLASSIFIED

3. REPORT TITLE

Abstract Reference List:
Reviews of Pertinent Literature in Shock.

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)

Technical Report.

5. AUTHOR(S) (First name, middle initial, last name)

L. B. Hinshaw

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
29 November 1976	41 (12) 520	88

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
N00014-76-C-0229	(14) TR - 113
b. PROJECT NO. NR 105-516	
c.	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
d.	

10. DISTRIBUTION STATEMENT

Distribution of this report is unlimited.

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
	Office of Naval Research

13. ABSTRACT

Brief summaries of recent pertinent literature in Pathological shock.

405916

DD FORM 1 NOV 65 1473 (PAGE 1)

S/N 0101-807-6811

UNCLASSIFIED
Security Classification

A-31408

OFFICE OF NAVAL RESEARCH
BIOLOGICAL & MEDICAL SCIENCES DIVISION
MEDICAL AND DENTAL SCIENCES PROGRAM, CODE 444
DISTRIBUTION LIST FOR TECHNICAL, ANNUAL AND FINAL REPORTS

Number of Copies	
(12)	Administrator, Defense Documentation Center Cameron Station Alexandria, Virginia 22314
(6)	Director, Naval Research Laboratory Attention: Technical Information Division Code 2627 Washington, D. C. 20375
(6)	Director, Naval Research Laboratory Attention: Library Code 2029 (ONRL) Washington, D. C. 20375
(3)	Office of Naval Research Medical and Dental Sciences Code 444 Arlington, Virginia 22217
(1)	Commanding Officer Naval Medical Research and Development Command National Naval Medical Center Bethesda, Maryland 20014
(1)	Chief, Bureau of Medicine and Surgery Department of the Navy Washington, D. C. 20375
(2)	Technical Reference Library Naval Medical Research Institute National Naval Medical Center Bethesda, Maryland 20014
(1)	Office of Naval Research Branch Office 495 Summer Street Boston, Massachusetts 02210

(1) Office of Naval Research Branch Office
536 South Clark Street
Chicago, Illinois 60605

(1) Office of Naval Research Branch Office
1030 East Green Street
Pasadena, California 91101

(1) Office of Naval Research
Contract Administrator for Southeastern Area
2110 G Street, N.W.
Washington, D. C. 20037

(1) Commanding Officer
Naval Medical Research Unit No. 2
Box 14
APO San Francisco 96263

(1) Commanding Officer
Naval Medical Research Unit No. 3
FPO New York 09527

(1) Officer in Charge
Submarine Medical Research Laboratory
Naval Submarine Base, New London
Groton, Connecticut 06342

(1) Scientific Library
Naval Medical Field Research Laboratory
Camp Lejeune, North Carolina 28542

(1) Scientific Library
Naval Aerospace Medical Research Institute
Naval Aerospace Medical Center
Pensacola, Florida 32512

(1) Commanding Officer
Naval Air Development Center
Attn: Aerospace Medical Research Department
Warminster, Pennsylvania 18974

(1) Scientific Library
Naval Biomedical Research Laboratory
Naval Supply Center
Oakland, California 94625

(1) Commander, Army Research Office
P. O. Box 12211
Research Triangle Park
North Carolina 27709

(1) Director, Life Sciences Division
Air Force Office of Scientific Research
1400 Wilson Boulevard
Arlington, Virginia 22209

(1) Commanding General
Army Medical Research and Development Command
Forrestal Building
Washington, D. C. 20314

(1) Department of the Army
U. S. Army Science and
Technology Center - Far East
APO San Francisco 96328

(1) Assistant Chief for Technology
Office of Naval Research, Code 200
Arlington, Virginia 22217