Endotoxin Shock: Correlation of Blood Coagulation and Leukocyte Ratios as Indices of its Progression and as a Basis for Therapy. BURTON M. ALTURA, PH.D., and S. G. HERSHEY, M.D., *Departments of Anesthesiology and Physiology, Albert Einstein College of Medicine, New York, N. Y.* Correlation of the clinical sequence of events with the mechanisms leading to cardiovascular collapse in gram-negative endotoxin shock is difficult and uncertain. The usual parameters, such as blood pressure, heart rate, central venous pressure, circulating blood volume, etc., are less reliable than for other types of shock. Need for reassessment of current regimes of therapy based on indices of both the course of the syndrome and the influence of therapy is repeatedly emphasized. The present study represents an attempt to develop relatively simple clinical indices of the course of experimental endotoxemia and its response to therapy. The indices are based on changes in the qualitative and quantitative interrelationships in whole blood coagulation and composition as well as differential leukocyte patterns during the progression of the syndrome. *Methods:* Rats were given single I.V. LD_{85} or LD_{50} doses of *Salmonella enteritidis* endotoxin. Serial (q. 30 min.) total and differential white blood cell (WBC) counts and clotting times were determined for a minimum of 6 hours. (Most fatalities occur within 7–8 hours.) Arterial blood pressure and mesenteric microcirculation (direct microscopy) were monitored in representative experiments. Survival was determined at 48 hours, at which time all animals were grouped as survivors or deaths for purposes of analysis. (Mean survival time was also determined for non-survivors.) Blood changes within and between groups in relation to time were analyzed rigidly by means of a computerized statistical analysis (Fortran Program). In addition, lymphocyte-to-granulocyte ratios (L/G) were calculated serially. More than 1,200 animals (involving more than 10,000 blood sample determinations) have been used to date. *Results:* Four distinct phases of change in blood pattern interrelationships emerged as identifiable, consistent parameters of the progression of endotoxic shock in rats. These phasic changes were such as to permit reliable and predictable differentiation between survival and death groups. L/G ratios as simple numerical derivations (phase 3) were remarkably accurate predictive indices of ultimate survival or death. The L/G ratios decreased progressively from 1.0 to 0.4 in survivors but remained at unity (1.0) in animals which subsequently died. Blood coagulability followed a predictable course which progressed to consistent total incoagulability in 5–6 hours (phase 4) in non-survivors only. Treated animals received various conventional agents (vasopressors, vasodilators, LMW dextrans etc.) alone or in combination at several intervals after the injection of the endotoxin. The influences of these agents on mortality rates and mean survival time were determined. *Summary:* In general, although the data in the therapy experiments are still incomplete, they indicate that when a particular therapeutic regime favorably alters survival and/or mean survival time the blood changes are also altered in the direction of those observed in untreated spontaneous survivors. These observations suggest that during the course of endotoxemia sequential (phasic) adjustment of specific thereapy, based on the blood picture and coagulation, may aid significantly in the rational development of regimes of therapy for gram-negative bacteremic shock. Aided in part by USPHS grants HE-09042, HE 11391.)

Methoxyflurane and Halothane Anesthesia During Controlled Bleeding in Dogs: Effect on Respiration. I. CARY ANDREWS, M.D., and LOUIS R. ORKIN, M.D., *Department of Anesthesiology, Albert Einstein College of Medicine, New York, N. Y.* Physiologic compensation for the metabolic acidosis associated with severe hemorrhage is dependent largely on the respiratory mechanism because renal function is virtually absent. There is little direct information, however, to explain the observation that whereas some animals succeed in increasing their respiratory tidal and minute volumes, others do not. Coincident to a previous study comparing the influences of halothane and methoxyflurane on survival of acutely bled dogs, differences were noted in their compensatory respiratory responses;

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/29/1/171/287601/0000542-196801000-00054.pdf by guest on 16 June 2021

these apparently related to the anesthetic used. A more critical comparison of methoxyflurane and halothane was therefore initiated to evaluate their possible roles in the ventilatory response to severe hemorrhage. *Method:* 20 unpremedicated dogs of comparable weights were anesthetized lightly with thiopental, 2 per cent, sufficient to allow for endotracheal intubation and cannulation of femoral vessels (skin infiltrated with lidocaine, 1 per cent). After the dogs had wakened completely, while breathing room air, blood volume (T-1824), arterial *p*H, P_{O_2}, P_{CO_2}, respiratory rate and minute ventilation were measured. Anesthesia was then instituted with either halothane or methoxyflurane to equipotent levels, based on the principle of minimum alveolar anesthetic concentration (MAC), adding only oxygen as diluent flow. Once MAC was reached, arterial blood samples, as above, were taken, ventilatory response to CO_2 was measured by removing the soda lime from the breathing circuit and adding minute measured amounts of CO_2, and a response curve was constructed. The animals were then bled 50 per cent of their measured blood volume in graded fashion over a 30-minute period, and all measurements were repeated. *Results:* In the *halothane* experiment, mean values before bleeding were: $P_{O_2} = 477$ mm. Hg, $P_{CO_2} = 39.1$ mm. Hg, $pH = 7.31$, base deficit $= -6.1$ mEq./l., respiratory rate $= 20$/min. and minute ventilation $= 3.9$ l. Mean values after bleeding were: $P_{O_2} = 431$ mm. Hg, $P_{CO_2} = 34.5$ mm. Hg, $pH = 7.26$, base deficit $= -10.5$ mEq./l., respiratory rate $= 32$/min., minute ventilation $= 7.1$ l. In the methoxyflurane experiments, mean values before bleeding were: $P_{O_2} = 470$ mm. Hg, $P_{CO_2} = 32.3$ mm. Hg, $pH = 7.33$, base deficit $= -8.1$ mEq./l., respiratory rate $= 18$/min., minute ventilation $= 3.8$ l. Mean values after bleeding were: $P_{O_2} = 453$ mm. Hg, $P_{CO_2} = 40.0$ mm. Hg, $pH = 7.23$, base deficit $= -10.9$ mEq./l., respiratory rate $= 24$/min., minute ventilation $= 3.8$ l. *CO_2 response* curves after hemorrhage during halothane anesthesia showed a fairly marked shift to the left and a slope indicating increased sensitivity of the respiratory center. During methoxyflurane, little if any significant changes were noted after hemorrhage. *Conclusions:* The preliminary findings in this study suggest that although halothane depresses respiration more than methoxyflurane in the normal animal breathing spontaneously, in the hemorrhagic shock state, the relative respiratory depressant effects of these agents are reversed.

Effect of Hyperthyroidism and Hypothyroidism on Halothane and Oxygen Requirements in Dogs. ARTHUR A. BABAD, M.D., *University of California Medical Center, San Francisco, Calif.* Hyperthyroid and hypothyroid patients have been thought to require more and less anesthetic, respectively, than normal patients. *Method:* To test the effect of these altered metabolic states upon halothane requirement, six euthyroid mongrel dogs were studied (q.v. below); these same six dogs were made hyperthyroid with dessicated thyroid, thyroxine and/or triiodothyronine and the studies were repeated; four of the six dogs were made hypothyroid with radioiodine and the studies were again repeated. At each metabolic level, the minimum alveolar concentration of halothane was determined (MAC, Eger *et al.*, ANESTHESIOLOGY *26:* 756, 1965); and oxygen uptake was measured at 3 multiples of MAC—approximately 2.0, 1.5 and 1.1 times MAC. Oxygen consumption at 1.5 MAC was chosen as the most reasonable reference point for comparing differences in metabolic activity in the various studies; anesthesia at 1.5 MAC was not so deep as to produce profound cardiovascular or respiratory depression, nor was it so light as to permit shivering and erratic ventilation. Body temperature was controlled during the MAC and oxygen consumption measurements. Mean body temperatures for all MAC and oxygen consumption studies were between 36.9 and 37.1 degrees C. Except for one (euthyroid) study in which one-third of the MAC measurement was carried out at 36.3 to 36.4 degrees C., all body temperatures were between 36.5 and 37.5 degrees C. *Results:* (1) Mean oxygen consumption at 1.5 MAC was 111.6 ± 13.1 ml./min./sq. m. in the euthyroid state; 140.7 ± 18.2 ml./min./sq. m. in the maximally hyperthyroid state; 72.8 ± 8.2 ml./min./sq. m. in the hypothyroid state. Mean euthyroid MAC closely approximated previously re-

Downloaded from http://pubs.asahq.org/anesthesiology/article-pdf/29/1/171/287601/0000542-196801000-00054.pdf by guest on 16 June 2021