

per cent, respectively. *Summary:* These findings suggest that prophylactic digitalization improves the inotropic state of the normal heart, especially the ability to develop the maximum force, during anesthesia. (Supported by USPHS Grant HE-01711 from the National Heart Institute.)

Effects of Halothane on Mitochondrial Oxygen Uptake: Site of Action. P. J. COHEN, M.D., B. E. MARSHALL, M.D., and J. LECKY, B.A., *Department of Anesthesia, University of Pennsylvania School of Medicine, Philadelphia, Penna.* *Methods:* Rat liver mitochondria were exposed for 20 minutes to halothane vaporized in air. Control mitochondria were treated similarly but exposed to air alone. In order to study reversibility, a portion of the exposed suspension was then equilibrated with air for an additional 20 minutes. Oxygen uptake was measured polarographically. Substrate (glutamate, 10 mM; succinate, 10 mM; and dihydronicotinamide adenine dinucleotide [NADH], 280 μ M), inorganic phosphate, 10 mM; oxygen, air-saturated reaction medium; and adenosinediphosphate, 250 μ M, were not rate-limiting. Since NADH does not penetrate intact mitochondria, the mitochondrial suspension was further treated by aging and resuspension in distilled water when NADH was to be substrate. *Results:* When *glutamate* was substrate, halothane produced a dose-related decrease in oxygen uptake. Halothane (0-10 per cent) had no effect on oxygen uptake when *succinate* was substrate. The effect of halothane on NADH oxidation was similar to that observed when *glutamate* was oxidized. In both cases inhibition was dose-related, was observed when less than 1 per cent halothane was administered, and was completely reversible provided that less than 3 per cent halothane had been used. Maximum inhibition (oxygen uptake 25 per cent of normal) was seen following exposure to 4 per cent halothane; concentrations greater than this had no additional effect. The addition of 5 mM amyral permitted the evaluation of amyral-sensitive oxygen uptake during NADH oxidation (*Exper. Cell. Res.*, Suppl. 3, 124, 1955). Addition of amyral to control mitochondria reduced oxygen uptake to 25 per cent of nor-

mal; this represents amyral-insensitive respiration. In mitochondria exposed to less than 4 per cent halothane, amyral resulted in a further diminution of respiration to 25 per cent of control. In mitochondria whose oxygen uptake had already been reduced to 25 per cent of normal by concentrations of halothane greater than 4 per cent, amyral produced no further changes. Similar findings were made when amyral was added to a suspension oxidizing *glutamate*. *Summary:* The action of halothane upon the mitochondrial respiratory chain is to inhibit NADH oxidation reversibly. Furthermore, since halothane inhibits only amyral-sensitive respiration, total oxygen uptake is not reduced below 25 per cent of normal by even high concentrations of halothane. (Supported in part by USPHS Grants GM-5-P01-09970-05, 5-T1-GM-215-01, 1-P01-GM-15430-01, and a grant from the Wellcome Trust.)

A Graphic Analysis of Cardiopulmonary Changes Following Major Surgery. F. J. COLGAN, M.D., and P. D. MAHONEY, M.D. *University of Rochester School of Medicine and Dentistry, Rochester, N. Y.* *Methods:* Twelve patients were studied before and after major upper abdominal surgery to determine the significance of any changes in cardiac output and FRC on intrapulmonary shunting. From this study, a method for the sequential plotting of changes in shunt in the critically ill patients was developed. Shunting was determined from simultaneously drawn samples of arterial and mixed venous blood and end-expired air. Cardiac output was determined by the Fick principle and FRC by closed-circuit helium dilution. *Results:* Prior to surgery, the mean total shunt breathing air was 22 per cent and the true shunt while breathing oxygen was 12 per cent. No change in mean total shunt, true shunt, or FRC occurred following surgery. Mean cardiac output for the group, however, was significantly reduced from 6 l/min to 4.8 l/min following surgery and marked individual variation in both cardiac output and $\text{CaO}_2\text{-C}\bar{\text{v}}\text{O}_2$ was noted. If these changes had not been taken into account in computing shunt, a significant underestimation of the mean total shunt would have

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been calculated preoperatively. Use of an assumed $\text{Ca}_{0_2}-\text{C}\bar{\text{v}}_{0_2}$ of 4.5 vol per cent, as is frequently done, would have led to both over- and underestimation of shunt by more than 50 per cent in several instances. *Summary:* Measurement of both $\text{Cc}_{0_2}-\text{Ca}_{0_2}$ and $\text{Ca}_{0_2}-\text{C}\bar{\text{v}}_{0_2}$ is necessary if a meaningful estimation of shunt is to be made in individual cases. Intrapulmonary ($\text{Cc}_{0_2}-\text{Ca}_{0_2}$) and systemic ($\text{Ca}_{0_2}-\text{C}\bar{\text{v}}_{0_2}$) oxygen content differences determine the intrapulmonary shunt: $\dot{Q}_s/\dot{Q}_t = \text{Cc}_{0_2}-\text{Ca}_{0_2}/(\text{Cc}_{0_2}-\text{Ca}_{0_2}) + (\text{Ca}_{0_2}-\text{C}\bar{\text{v}}_{0_2})$. With $\text{Cc}_{0_2}-\text{Ca}_{0_2}$ on the Y axis and $\text{Ca}_{0_2}-\text{C}\bar{\text{v}}_{0_2}$ on the X axis, the relative influence of pulmonary and systemic factors on shunting can be readily determined. A series of straight lines representing per cent shunt are determined by substitution in the above formula; these radiate from the XY intercept. Since shunt values obtained using oxygen content differences as coordinates are not affected by the absolute value of the inspired oxygen tension, serial plotting of shunt values allows better assessment of cardiopulmonary therapy.

A Safer Method for Measuring Body-fluid Compartments in Patients. D. R. COOK, M.D., S. J. GALLA, M.D., and W. S. GUALTIERE, PH.D., *Departments of Anesthesiology and Physical Education, University of Pittsburgh, Pittsburgh, Penna.* Measurement of body-fluid compartments requires the administration of relatively high doses of radioactive tracers. Ordinarily, 10 μc of ^{125}I iodine are used to measure plasma volume; 20 μc of ^{51}Cr chromium are used to measure erythrocyte mass; 70-100 μc of ^{35}S sulfur are used to measure extracellular fluid volume; 1.0 of tritium is used to measure total body water. Although this represents a total body radiation exposure of only 0.402 rems, the testicular and thyroid exposure from the radioactive sulfur and iodine is 2.925 rems. Recently, liquid scintillation spectrometry has provided increased simplicity and accuracy in the measurement of the activity of the weak beta emitters. *Methods:* We devised a technique to reduce radiation exposure significantly, using a double-labeling liquid scintillation technique with quench cor-

rection. *Results:* We were able to reduce the ^{35}S sulfur dose to 10 μc and the tritium dose to 0.5 mc per subject. Plasma volume and blood volume were measured with the Evan's blue-microhematocrit method, eliminating ^{125}I iodine and ^{51}Cr chromium. Total body radiation was reduced 72 per cent and the radiation exposure to the testes and thyroid was reduced 98 per cent. Our method was validated by measuring body fluid compartments in young men. The volumes obtained were comparable to those reported by Moore for men in the same age group. (Supported in part by USPHS Grant GM-13965.)

Cardiovascular Effects of Cyclopropane in Man. D. J. CULLEN, M.D., E. I. EGER, II, M.D., and G. GREGORY, M.D., *Department of Anesthesia, University of California, San Francisco Medical Center, San Francisco, California.* Simultaneous cardiac and peripheral vascular effects of cyclopropane were determined in nonmedicated volunteers, at normal Pa_{CO_2} and body temperature. *Methods:* Measurements were made with the subjects awake during controlled ventilation (Pa_{CO_2} 34 mm Hg) and at 15-20, 25-30 and 35-40 per cent alveolar cyclopropane (Pa_{CO_2} 38-40 mm Hg). *Results:* Cardiac output (\dot{Q}), heart rate (HR) and stroke volume (SV) remained at or near control values except at 35-40 per cent cyclopropane, when a 15 per cent decrease in \dot{Q} occurred ($P < 0.05$). Mean arterial pressure (MAP), total peripheral resistance (TPR) and mean right atrial pressure (MRAP) rose significantly with onset of cyclopropane anesthesia. TPR and MRAP continued to rise as cyclopropane concentration increased. The peripheral vasculature showed arterial and venous constriction because forearm vascular resistance (FVR) increased while forearm venous compliance (FVC) decreased. When cyclopropane was acutely reduced from 35 per cent to 15 per cent, an overshoot of \dot{Q} , MAP and SV developed in the first two minutes. This overshoot reversed itself as MRAP continued to fall at ten minutes. *Summary:* We suggest that ventricular function is altered by cyclopropane because of the profound rise in