groups are not important for the action of the three enzymes which are not affected by the reagent. Since doubling the formaldehyde concentration still does not inhibit these three, it is probable that the latter explanation is correct. Finally it may be mentioned that the formaldehyde inhibition of the succinoxidase is the same at pH 6.0 as it is at pH 8.0.

Summary. 1) Formaldehyde inhibits the succinic acid, choline, L-proline and sarcosine oxidases in liver homogenates. In equal concentrations, it has no effect on the amine and cytochrome oxidase of liver or the D-amino acid oxidase of kidney. 2) The prior addition of substrate protects the enzymes from the formaldehyde for a short period of time.

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Can Experimental Shock be Induced by Coronary Occlusion?* (18414)

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Objectives of the Experimental Approach. Of the several hazards of coronary occlusion, the clinical development of a shocklike state has been discussed a good deal in recent years. The clinical inference that this is due to supervention of peripheral circulatory failure has not, however, received valid support. Experimental work appears to favor the conclusion that circulatory failure not attributable to severe irregularity of the heart beat is due successively to defection of useful contractions in the ischemic area, loss of total contractile energy through expansion of the affected area, and failure of the still viable fractions to compensate adequately(1-4). However, such conclusions are based on experiments extending only an hour or so beyond the time of coronary occlusion, after which the animals usually die due to ventricular fibrillation. Thus the most complete dynamic study of changes in intraventricular and aortic pressure pulses, that of Orias(2), stressed chiefly (a) that occlusion of the ramus descendens anterior is followed immediately by hypodynamic beats with shortened systoles, but (b) that these effects are usually compensated within 4 to 7 minutes through increase in initial tension in the left ventricle, which restores aortic and left ventricular pressures to normal levels. This compensation failed to occur in only three of 23 experiments and in these rapid dilation and failure of the heart supervened. The subject has also been studied on survival animals of which the report by Gross and his associates(5) may serve as an illustration. These investigators found, in dogs that survived for a day or more, a decrease in cardiac output, some irregular decline of arterial pressure, and evidence of pulmonary congestion based on a prolonged cyanide time. Since they were unable to establish any reduction in blood volume or fall in peripheral venous pressures they concluded that evidence for peripheral circulatory failure was lacking.

Despite the negative character of previous experimental work it seemed important that another attempt be made to determine whether hemodynamic signs of peripheral circulatory failure develop in animals which have survived occlusion of the ramus descendens anterior for 5 hours or more and in which serious arrhythmia has been prevented or mini-

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mized as a contributory factor to the circulatory failure.

Methods and Technics. Dogs anesthetized with 3 mg/kg of morphine and 200 mg/kg sodium barbital were used. The chest was opened and the heart exposed. Right and left atrial and aortic pressures were recorded by calibrated Gregg type manometers of suitable sensitivity and adequate frequency. Following the surgical procedures and cannulations, the animals were allowed to stabilize for an hour before occlusion of the ramus descendens anterior was attempted. In some animals control blood volume determinations or cardiac output determinations by the Fick method were made during this period, followed by subsequent determinations during later phases of the experiment, as described below. Standard technics were used for all of the foregoing procedures. Since the supervention of long periods of marked arrhythmia, such as frequently follow coronary ligation in dogs, can itself lead to an imbalance of the circulation which reduces cardiac output and arterial pressures, it was obviously important to prevent such irregularities if the development of myocardial or peripheral circulatory failure was to be assessed. Several expedients proved helpful in warding off such attacks in approximately half of the dogs used. Care was exercised to avoid accidental mechanical stimulation of the ventricles which are supersensitive and often respond by runs of premature systoles. The method of partial occlusion followed by complete occlusion in 30 minutes described by Harris(6) was found only moderately successful. Better results were usually obtained by intravenous administration of quinidine sulfate, 0.5 mg/kg. In earlier experiments quinidine was administered as soon as any ectopic beats appeared; subsequently, the drug was given about 15 minutes prior to coronary occlusion. When slowly given, such doses had no demonstrable effects on atrial or aortic pressure.

Results. Through adoption of the foregoing expedients, 11 experiments were realized in which irregularities were successfully avoided or were very transient in nature. In these, the hemodynamics due to myocardial or peripheral circulatory default could be studied for 5 to 7 hours after ligation of the ramus descendens anterior. Since other shock-provoking agents used in equivalent experiments on similarly anesthetized dogs with exposed hearts always cause irreversible failure involving the peripheral circulation in less than five hours, such a time span seemed sufficient for hemodynamic evidence of such failure to become manifest. Contrary to expectations, only one of the animals studied showed evidences of serious circulatory failure.

Blood volume and cardiac output changes. Blood volume determinations were made by the Evans' blue technic in all of the 11 animals during the preliminary stabilization period and again at the close of the experiment, 6 to 7 hours after coronary occlusion. In none of these were significant changes found. In 5 dogs cardiac output determinations were made by the direct Fick method during the control period, 45 to 60 minutes after ligation and again 5 hours after ligation. Comparisons were also made with output evaluations by the pulse contour method(7, 8). These results are summarized in Table I. In the first 2 experiments in which aortic pressures and pulse forms remained normal, no significant reduction in cardiac output (Fick) was evident. In the third experiment listed, significant reduction in cardiac output (Fick) supervened toward the close of the experiment owing to the supervention of ventricular alternation. In the fourth experiment listed, alternans of varying degrees occurred throughout the observation periods; the early reduction of cardiac output, however, did not persist; the output volume recovered at the end of 4 hours. In the fifth experiment listed, significant hypotension had developed at the end of a 5½ hour period, and cardiac output was decreased.

In order to compare changes in cardiac output determined by the Fick method with those of pulse contour method under normal

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TABLE I. Cardiac Output in Liters/min./sq.m. Before and After Coronary Occlusion.

Exp. No.	Fick	Terminal changes	Pulse contour method	Terminal changes	Time in relation to coronary ligation
13*	2.88		2.24		Control
	2.39		1.82		1 hr
	2.68	—0.20	2.01	—0.23	5 hr
31	2.39		3.25		Control
	2.34		2.78		30 min.
	2.26	—0.13	4.12	+0.87	4½ hr
27	1.94		2.28		Control
	1.32		1.81		1 hr
	0.88†	—1.06	1.75	—0.53	5 hr
19	2.38		2.20		Control
	1.98†		2.13†		45 min.†
	2.05†	—0.33	2.10†	—0.10	4 hr†
24	1.98		3.84		Control
	1.07		2.52		45 min.
	1.18	—0.80	3.43	—0.41	5½ hr (hypotension)
21	1.82		1.78		Control
22	2.67		1.74		"
26	2.12		2.20		"
12*	1.55		3.25		"
	2.40	+0.85	3.40	+ .15	Post-ligation
H-F 1	1.30		1.34		Control
	1.64		1.52		"

* A-V oxygen differences determined in duplicate by Scholander method, checking by 0.2 vol. %—others in duplicate by method of Peters and Van Slyke, checking within 0.1 vol. %.
† *Pulsus alternans*, spontaneous.

conditions, 5 other experiments are added in Table I in which observations could not be completed owing to supervention of fibrillation. Excellent agreement in estimation of control cardiac outputs is noted in Exp. 19, 21, 26, and HF-1 in which the pulse contour method yielded outputs deviating from Fick determinations by only +.08 to −.18 L./min. In the other six control determinations the deviations of the pulse contour values ranged from −.093 (Exp. 22) to + 1.86 (Exp. 24) L. min. Such deviations support the conclusion of previous work from this laboratory (9) that the method of Hamilton and Remington cannot be relied upon for quantitative estimations of cardiac output and calculation of TPR even under normal conditions. In Exp. 12, 13, 19, 24, and 27, in which normal pressure ranges and contours were maintained, the directional changes in cardiac output determined by the pulse contour method corresponded qualitatively. However, in Exp. 31 the quantitative and directional changes deviated considerably.

Aortic and Atrial Pressure Changes. The segments of original records in Fig. 1 serve to show the nature of the left and right atrial pressure changes up to 7 hours after ligation of the left anterior descending ramus and also indicate in segment B the method used in measurement of atrial pressures. Measurements were made (a) of the instantaneous pressures at the end of diastole (Z point) which should be equivalent to the initial pressures in the ventricles, and (b) of the pressure near the end of systole (V point) which is a criterion of the extent to which the atria fill during ventricular systole. (For details see Little *et al.*)(10). All such measurements were made at comparable phases of respiration and the illustrative records represent such selected pressure pulses. In Fig. 1, segment A represents a record taken at the end of the one hour control period. Segments B to D illustrate the pressure changes 1, 30 and 60 minutes after coronary occlusion. Obviously, records taken immediately after coronary occlusion show that systolic, diastolic, and pulse pressures decrease somewhat, the aortic pressure rises more gradually, and the

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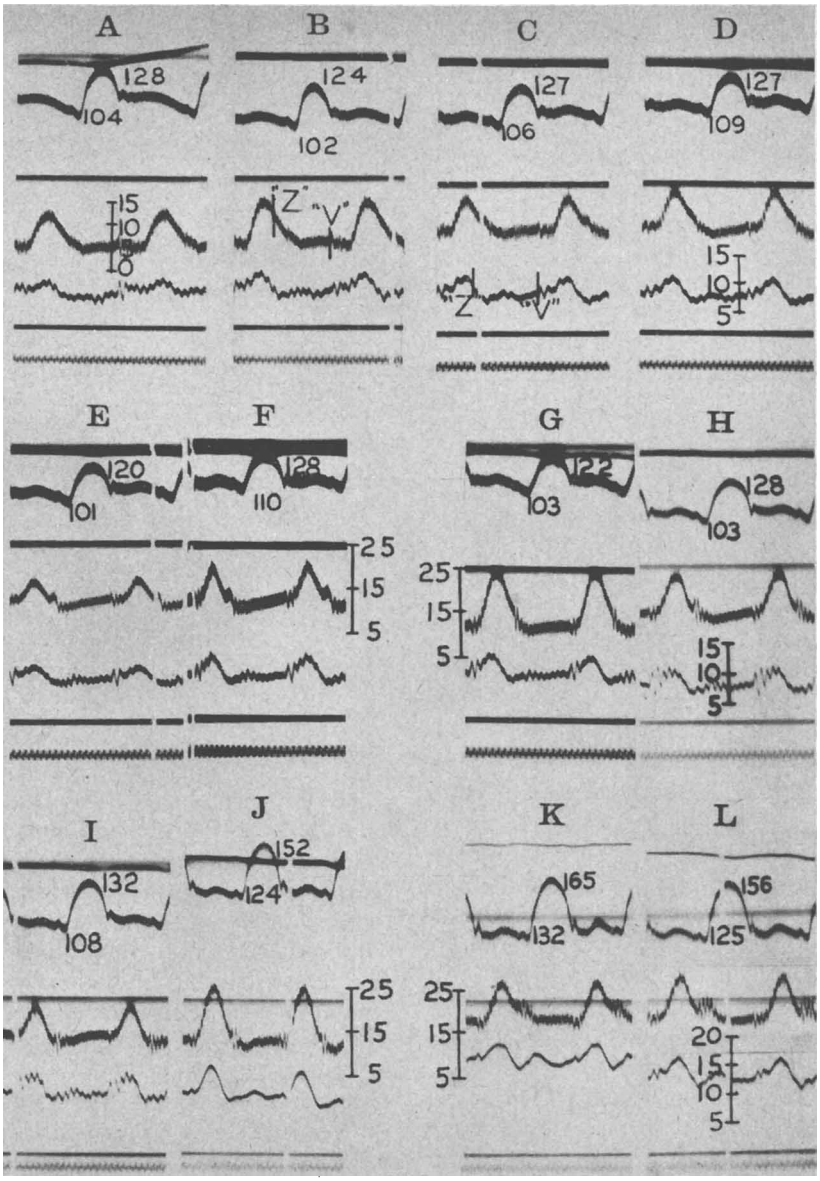

FIG. 1.

Segments of records showing changes in aortic (upper), left atrial (middle), and right atrial (lower) pressures before (A) and at various times after coronary ligation. Post-ligation times: B, 1 min.; C, 30 min.; D, 60 min.; E, 2 hours; F, 3 hours; G, 4 hours; H, 5 hours; I, 6 hours; J, 7 hours; R, 2 min. after infusion; L, 5 min. after infusion. Calibration scales for aortic pressure in mm Hg; for atrial pressures in cm saline. Discussion in text.

systolic ejection is abbreviated. It requires no calculations to state with assurance that systolic discharge is immediately reduced and with it cardiac output/min., despite the slight cardiac acceleration. There is a rather prompt recovery from this hypodynamic state of the left ventricle and at the end of an hour (segment C) aortic pressure pulses and the duration of systolic ejection have resumed pre-ligation shapes and values. All of these ob-

servations during the first hour accord with the findings of Orias reported from this laboratory(2). Our chief interest focuses in the changes in atrial pressures during this period. It may be noted that left atrial pressure rises almost immediately and continues to increase both at the Z and V points, whereas pressure in the right atrium shows no significant changes.

Segments E, F, and G illustrate the dynamic conditions at the end of the second, third, and fourth hours respectively. Arterial pressures are relatively well maintained but the pulse pressure is reduced slightly, and the pressure pulse displays a slower rise and more rounded contour. However, in segments H, I and J the pressure pulses indicate continued improvement in systolic discharge. In fact, 7 hours after ligation (J) arterial pressures and pressure pulses exceed those during the control period (A). The only similarity to pressure pulses observed with low systolic discharge in shock is the flattening of the diastolic limb; but its significance has never been satisfactorily clarified. Considerable unexplained variation takes place in the amplitude of the atrial wave (*cf.* segment E and I with G. H. J). However, Z and V pressures proved to be affected very little by these variations. All records revealed persistence of an elevated atrial pressure. These changes conform to the concept that compensation by viable myocardium of the left ventricle is achieved through an increase in atrial filling pressure and a resultant stretch of the left ventricle.

In order to determine whether the limit of cardiac competency to increased filling and stretch was approaching a limit at the end of 7 hours, a femoral infusion of 200 cc of blood was given within 2 minutes. Segments K and L depict the reactions 2 to 5 minutes after completion of the infusion, and the graph of Fig. 2 shows the pressure changes. The aortic pressure pulses definitely show that systolic discharge was augmented; however, the flattened diastolic limb and larger dicrotic wave persist. Pressures are immediately elevated at the Z and V points in both atria (K), but while right atrial pressure has declined within 5

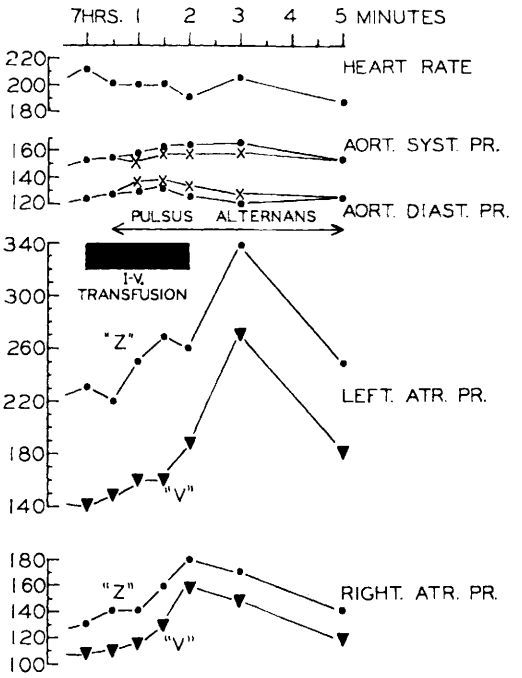

FIG. 2.
Graphs showing minimal changes in heart rate/min. and pressures during and after transfusion of same animal, as shown in Fig. 1. Scales as in Fig. 1.

minutes, left atrial pressure remains elevated (J), indicating that the ability of the left heart to respond to increased stretch has not been exceeded as a result of the infarction. However, as indicated in the graphs of Fig. 2, ventricular alteration was induced. It may be added parenthetically that had right atrial pressure alone been recorded, the inference might have been drawn that the maintenance of the systolic discharge of the left ventricle bears no relation to atrial pressure, and that therefore Starling's law is inapplicable. Cardiologists who have drawn such conclusions on the basis of catheterization studies may have fallen into similar traps.

The foregoing types of reactions in which left atrial pressures were elevated promptly after ligation and remained high, while right atrial pressures continued near normal levels, was characteristic of six of these experiments. In only one of these experiments, illustrated in Fig. 3, did signs of circulatory failure, characterized by reduction in systolic, diastolic, and pulse pressures, supervene after the

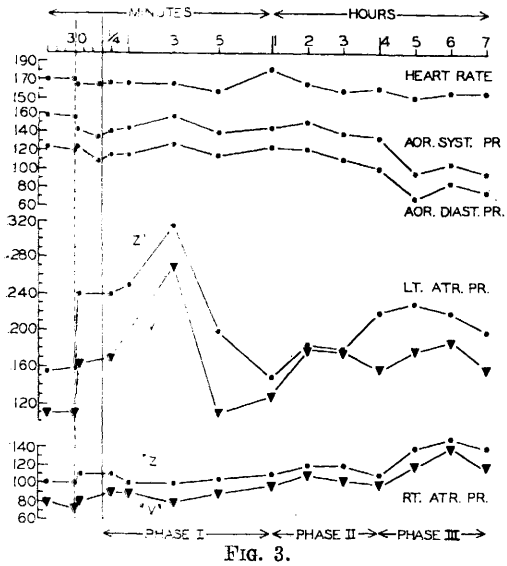

FIG. 3.

Plot of data showing changes in heart rate/min., aortic and atrial pressures after coronary occlusion. Scales as in Fig. 1. Discussion in text.

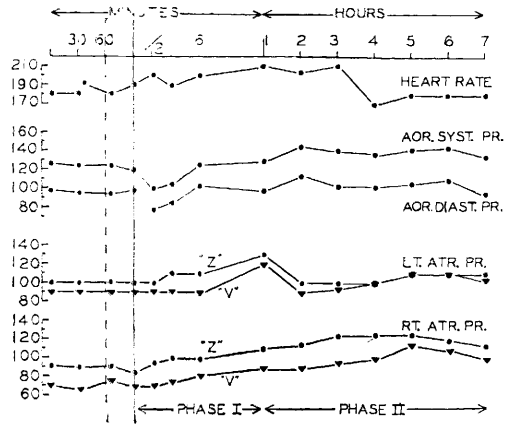

FIG. 4.

Plot of data showing changes in heart rate/min., aortic and atrial pressures after coronary occlusion. Scales as in Fig. 1. Discussion in text.

third hour (Phase III). Since this was accompanied by a marked increase both in right and left atrial pressures, the inference is that failure was of cardiac and not of peripheral origin.

In 5 other experiments pressures in the 2 atria followed a different trend. Left atrial pressure either returned to control levels after an initial increase, or displayed no initial elevation and only a delayed slow increase. Figure 4 illustrates such a lag in the rise of left atrial pressure immediately following ligation, but at the end of an hour it was definitely elevated. In these cases right atrial pressure increased progressively from the start, indicating that reduction of venous return characteristic of shock could not be involved. On the contrary, under the stimulating influence of the augmenting atrial pressures and increased diastolic stretch, the right ventricle maintained an adequate return to the left ventricle and an adequate systolic discharge, as evidenced by the maintenance of good aortic pressure and an increase in pulse pressure.

Discussion. No lengthy discussion of the results presented is required. Blood volume determinations in 11 animals showed no significant changes from control values. Cardiac output was reduced only in animals when they developed ventricular alternation. The fact that right atrial pressures did not decrease at any time up to seven hours indicates that venous return is not decreased. Hence there was no evidence that circulatory failure of peripheral origin supervened. With a single exception, aortic pressure pulses also gave no evidence that the output of the left ventricle was impaired even when submitted to added strain of transfusion.

The results presented indicate clearly that changes in the dynamics of the left ventricle cannot always be gauged by measurement of pressure in the right atrium. Furthermore, it is quite generally recognized that alterations in peripheral venous pressure may be wholly misleading, for they do not necessarily correspond to absolute changes in right atrial pressures.

Summary and conclusions. The left ramus descendens anterior of the exposed hearts of dogs was ligated, arrhythmia was prevented by use of small doses of quinidine, and records of aortic, left atrial and right atrial pressures were repeatedly recorded by calibrated Gregg-type manometers for 5 to 7 hours. Blood volume and cardiac output determinations were made in some animals. The results indicate that up to 7 hours there is no evidence, on the basis of an analysis of cardiac output, blood volume and pressure pulses, that circulatory failure of peripheral origin super-

venes in dogs after ligation of a major coronary branch.

Comparison of cardiac output data obtained by the Fick method and the aortic pulse contour method showed sufficient disagreement to indicate that the latter method is not sufficiently accurate for quantitative evaluation of cardiac output, even when pressure pulses of normal contour and normal aortic pressures prevail.

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Effect of Adding Carbon Dioxide to Inspired Air on Consciousness Time of Man at Altitude.* (18415)

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Accurate appraisal of the factors which influence useful consciousness states in flyers under hypoxic stress is of fundamental importance in aviation. The duration of consciousness of subjects breathing ambient air of normal composition at various altitudes has been reported by several investigators (1-3). A method which gives a critical end point for loss of useful consciousness has also been described(4). The following reports extend the range of studies to include the addition of carbon dioxide to the normal composition of inspired air. Such a situation may at times exist in aircraft flying at high altitudes.

It is apparent from the paper by Fenn *et al.* (5) that the additions of carbon dioxide to inspired air containing nitrogen will have a beneficial effect on subjects at altitude. Otis *et al.*(6) have shown, however, that carbon dioxide added to inspired oxygen does not increase the tolerance of mice and men at altitude. Because of the complexity of the physiological processes involved one cannot safely predict as to the quantitative effect of carbon dioxide on consciousness time. Consequently, an experiment was designed to determine the effect of certain concentration of carbon dioxide on the duration of consciousness at 30,000 (226 mm Hg) and 35,000 feet (179 mm Hg) simulated altitudes.

Procedure. The time of useful consciousness was determined under conditions where the ambient pressure in a decompression chamber was maintained constant and the subjects changed from breathing pure oxygen to breathing gas mixtures from Douglas bags. Gas mixtures were made in a large spirometer and transferred to Douglas bags just previous to ascent. It should be noted that the partial pressure of oxygen in the inspired air was kept constant and that the addition of carbon dioxide was not made at the expense of oxygen. In other words a calculated quantity of oxygen was added with the carbon dioxide to correct for the dilution effect. Analyses during experiments confirmed the accuracy of the gas mixing procedure. Thus uniform partial pressure of oxygen existed in the inspired air of both control and experimental tests. Gas analyses were made in 2 ways. Samples of air delivered to the mask were analyzed by means of a Haldane gas analyser. A Pauling oxygen meter was also employed to determine the partial pressure of oxygen which was kept constant within $\pm$ 1 mm Hg. Carbon dioxide

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