to its C. F. content and not to free folic acid possibly present as a contaminant or formed by the action of the hydrogen ion on the C. F. preparation.

Since 1 cc of the C. F. preparation containing 3.0 million C. F. units had a folic acid activity equivalent to approximately 1.0 mg of PGA as determined by microbiological assay with *S. fecalis,* 0.42 cc of the preparation, containing 1.25 million units, had a folic acid activity corresponding to 0.42 mg of PGA. Thus the preparation was 36 to 72 times as potent in preventing the antileukemic effects of 4-amino-N^{10}-methyl-PGA as could be expected from its total folic acid activity.

Summary. The effect of 4-amino-N^{10}-methyl-PGA in prolonging the survival time of mice with transplanted leukemia AK4 can be blocked almost completely by prior administration of 1/3 to 2/3 as much by dry weight of a preparation of citrovorum factor. Thus, citrovorum factor is at least 12 to 24 times as active as pteroylglutamic acid in preventing the antileukemic effect of 4-amino-N^{10}-methyl-PGA.

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Pressure Gradients in the Atria and Pulmonary Veins in Man. (18032)

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Careful analysis of the pressure records obtained from the pulmonary veins and chambers of the heart was carried out on 4 non-cyanotic persons selected because of their varying anatomic and physiologic defects. In each instance, the pressure in the pulmonary vein was found to be higher than pressures measured in either or both atria. The cases form a unique group: in 2 the pulmonary vein, being anomalous, drained into the superior vena cava and the right atrium respectively; in 1 there was an atrial septal defect with a large left-to-right shunt; and in the fourth there was a patent foramen ovale, without demonstrable shunt, associated with moderate pulmonary stenosis. The observations on the pressure gradients are in accord with the early reports of Cournand and associates(1) and of Dexter and associates(2,3), who reported their findings in patients with atrial septal defect. One of the purposes of this study was to investigate, by detailed examination of pressure pulses, the concept that the gradient of pressure producing flow of blood from left to right atrium results from pressure transmitted through the pulmonary circulation by the right ventricle. This view was not expressed by Little and associates(4).

Methods. Records of the 4 patients adequate for analysis were obtained over a short sequence of time from various cardiac chambers. In each instance the tip of the cardiac catheter entered a pulmonary vein and was confirmed in a position several centimeters distal from the atrial opening by roentgenography. Recorded pressure and oxygen content of a sample of blood were also measured with the catheter tip in the same location.

Simultaneous records of blood pressure, of respiratory cycle and of electrocardiogram were made in each instance except in Case 1, in which respiration was not recorded. For measurement of pressure a strain gauge manometer was attached to the external end of the catheter. The reference point of zero pressure was located at the midpoint of the thorax at the level of the third rib at the

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TABLE I.
Pressures in Millimeters of Mercury Measured at Indicated Points in One Cardiac Cycle, Through Catheter in Pulmonary Vein (P.V.), Left Atrium (L.A.), and Right Atrium (R.A.).

Phase of cardiac cycle	Case 1			Case 2			Case 3		Case 4	
	Phase of respiration									
	Midinspiration			End expiration			End inspiration		Midexpiration	
	P.V.	L.A.	R.A.	P.V.	L.A.	R.A.	P.V.	R.A.	P.V.	R.A.
Onset of P wave	10.3	5.9	6.7	6.9	2.6	1.3	3.3	—2.6		
0.1 sec. before R wave									9.2	3.7
Mid P-R interval	6.8	7.4	8.2	3.8	0	1.7	3.2	—0.3		
Onset of R wave	13.1	8.9	9.3	3.7	4.1	0.7	4.7	1.4	10.0	5.6
Mid R-T interval	10.3	3.9	3.6	1.2	0	—0.4	2.4	—2.9	10.7	8.8
End of T wave	10.8	10.1	6.8	5.3	1.9	1.4	3.5	0	14.8	5.6
Midpoint of electrical diastole	10.4	8.4	9.2	7.0	2.0	1.9	6.2	1.4		
0.1 sec. after T wave									16.1	8.2
	—	—	—	—	—	—	—	—	—	—
Avg	10.3	7.4	7.3	4.6	1.8	1.1	3.9	—0.5	12.2	6.4

sternal border.

In order to achieve comparable data for pressures which were not measured simultaneously, single cardiac cycles of reasonably equal length and occurring in the same period of the respiratory cycle were selected for detailed measurement from the photographic record made in each cardiac chamber and great vessel. In Case 1, wherein a record of respiration was not made, comparable cardiac cycles were chosen from the record on the basis of pressure relationships noted on those records in which respiratory tracings were present. Measurements of the pressure recordings were made at the following phases of the cardiac cycle: onset of P wave, mid P-R interval, onset of R wave, midpoint of R-T interval, end of T wave, and midpoint of electrical diastole, except in Case 4 in which auricular fibrillation was present and measurements could not be made at the first two sites (Table I). An example of the type of record from which this study was made appears in Fig. 1. These pressure tracings were taken from Case 2 wherein the catheter entered all 4 cavities of the heart.

In order to eliminate possible error due to failure to achieve comparable phases of respiration in selecting cardiac cycles, pressures were compared in Cases 2 and 3 both in end expiration and in end inspiration. In Case 4 pressures were also recorded in midexpiration and in midinspiration. The gradients of pressure were found to be consistent in all cases.

Results. Catheterization of the heart in Case 1 yielded evidence for an atrial septal defect with left-to-right shunt. The average gradient between pulmonary vein in the lung and left atrium proved to be 2.9 mm of mercury, between pulmonary vein and right atrium 3.0 mm (Table I). The calculated flow through the pulmonary circulation was 15.3 liters per minute.

Catheterization of the heart in Case 2 revealed a patent foramen ovale without demonstrable shunt (no arterialization of blood in the right atrium). A ventricular septal defect and mild pulmonary stenosis were also present. The average gradient between pulmonary vein within the lung and left atrium,

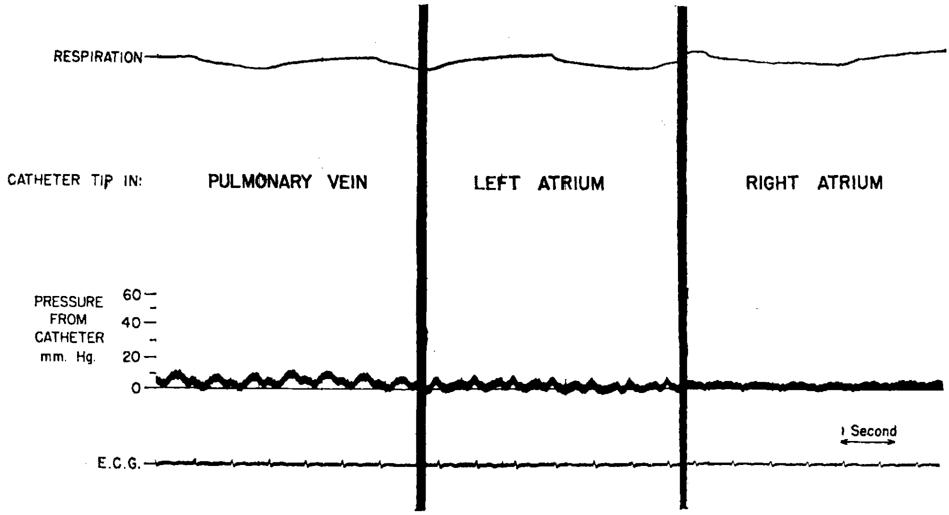

FIG. 1.
Low pressure tracings recorded through catheter with tip in sites indicated (Case 2).

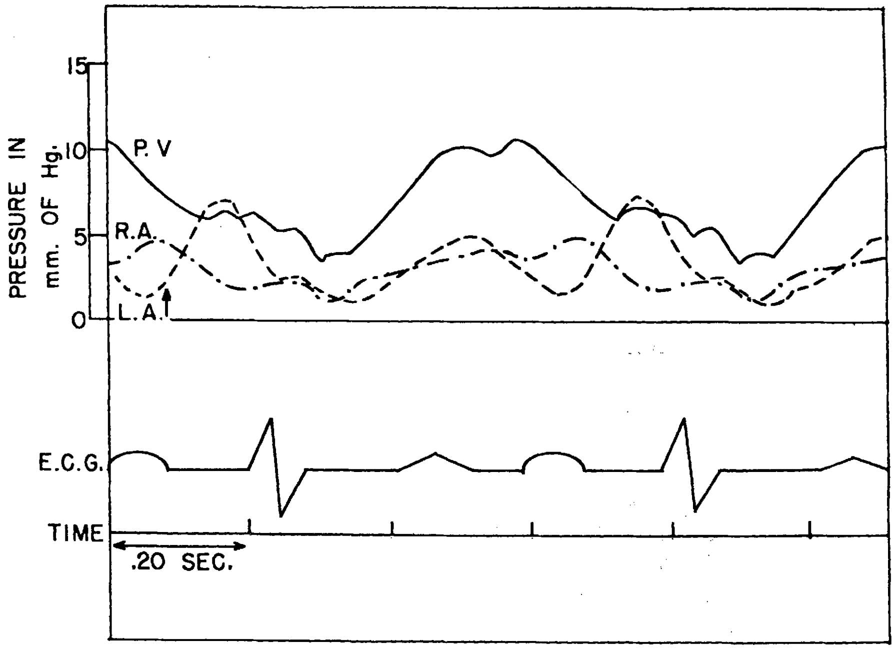

FIG. 2.
Superimposed tracings from fivefold photographic enlargements of the pulse contours recorded during one cardiac cycle in pulmonary vein (P.V.), right atrium (R.A.), and left atrium (L.A.) (Case 2). All cycles selected in midexpiration.

at the end of expiration, was in this case 2.8 mm of mercury, between pulmonary vein and right atrium 3.5 mm (Table I). The flow through the pulmonary circulation as measured by the direct Fick principle was 9.2 liters per minute.

In the catheterization procedure on Case 3 a right pulmonary vein was entered from the lower portion of the superior vena cava. The average gradient between pulmonary vein and right atrium was 4.4 mm of mercury (Table I). The calculated flow through the pulmonary circulation was 11.7 liters per minute.

Catheterization of the heart in Case 4 revealed an anomalous pulmonary vein draining into the upper part of the right atrium. The average pressure gradient between pulmonary vein and right atrium was 5.8 mm of mercury (Table I). The pulmonary flow was 12 liters per minute.

Comment. In the 4 cases studied, a pressure gradient between a pulmonary vein several centimeters distal to the atrial opening and either or both atria during the major portion of the cardiac cycle was demonstrated. This gradient is illustrated in Fig. 2, which consists of tracings selected at midexpiration from the actual records from pulmonary vein and atria in Case 2. The illustration was prepared by tracing fivefold photographic enlargements of the pulse contours during a cardiac cycle. The average pressure gradient between pulmonary vein and right atrium in the 4 cases studied was 4.2 mm of mercury. This value compares well with those previously reported in the literature(1,2,5).

Possible sources of error in measurement of pressure require comment in this study because of the relatively small differences observed. One likely source could result from differences in the position of the catheter tip relative to the arbitrarily selected zero point of midthoracic position. But error due to this factor does not seem likely to account for the consistent differences in pressures observed.

Of greater possible significance as a source of error is the position of the orifice of the catheter relative to the flow of blood. A model was built in order to investigate this end pressure effect. A No. 8 catheter was mounted in a glass tube 1 meter in length with an internal diameter of 1 cm, which was connected through rubber tubing to a water faucet. The pressures were recorded photographically by two 0.2 lb strain gauge manometers; one was connected to the catheter, the other to a T tube sealed perpendicularly into the side of the 1 cm glass tube near its midpoint. Simultaneous recordings of pressures were taken at different flow velocities. An analysis of the pressure tracings showed that a flow velocity of 80 cm per second directed against the open orifice of the catheter was required to produce a pressure 2.5 mm greater than the true lateral pressure. These data agree with those of Haddy and Visscher(6), who made a similar experiment using a No. 10 catheter.

In Case 1 of this series, in which there was the greatest amount of shunt, the pulmonary flow calculated by the direct Fick principle was 15.3 liters per minute. Assuming that this flow was distributed equally in four pulmonary veins and that the diameter of the pulmonary vein catheterized was 1.3 cm, the lower limit of values for the diameter of normal pulmonary veins measured by Charpy (7), the velocity of flow in this vessel would be 48 cm per second. According to the data obtained on the model built in this laboratory, a flow of this magnitude could account for a pressure only 0.8 mm of mercury greater than true lateral pressure. The observed difference in pressure in Case 1 between pulmonary vein and the left atrium, in which the position of the orifice with respect to flow was not clear, proved to be 2.9 mm of mercury. In Case 2, in which pulmonary flow was but 9.2 liters per minute, the lowest pulmonary flow of the 4 cases, the end pressure effect in a vein 1.3 cm in diameter could account for but 0.5 mm of mercury difference whereas the recorded difference in pressure between pulmonary vein and left atrium was 2.8 mm of mercury. It does not seem likely, therefore, that an end pressure effect was the only phenomenon being observed in the cases reported.

Furthermore, the pressures recorded from the venae cavae were significantly lower than those observed in the pulmonary veins, and there was a consistent difference in inflow pressure into the two atria averaging 6 mm of mercury in these cases. It must also be noted that the measurements taken with the present technics are in agreement with those

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of other authors using different methods. Hamilton and associates(8), measuring pressures with a needle directly inserted into the vessels of normal unanesthetized dogs breathing quietly, recorded in the pulmonary veins average pressures of 3 to 12 mm of mercury. In this study, average pressures recorded in the pulmonary veins were 3.9 to 12.2 mm.

A lesser distensibility of the left atrium cannot account for the high pressures observed in the pulmonary veins draining into vena cava and right atrium.

Summary. 1. During cardiac catheterization, a pressure gradient was found between a distal point in a pulmonary vein and either or both atrial chambers during the major portion of the cardiac cycle in 2 cases of atrial septal defect, in a third case wherein an anomalous pulmonary vein drained into the right atrium, and in a fourth in which an anomalous pulmonary vein emptied into the superior vena cava.

2. The magnitude of the gradient between pulmonary vein and *right* atrium varied from 3.0 to 5.8 mm of mercury with an average value of 4.2 mm in the 4 cases studied.

3. Evidence that this gradient could not be entirely due to an end pressure or Pitot effect was obtained from study of a model in which the end pressure effect was shown to be 0.5 to 0.8 mm of mercury at the same calculated flow velocities.

4. It is suggested that this pressure gradient is a result of the pressure transmitted by the right ventricle through the pulmonary circulation, and is an important factor in the left-to-right shunt observed at rest during quiet breathing in uncomplicated cases of atrial septal defect.

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Effect of Choline Chloride on Development of Atherosclerosis in the Rabbit.* (18033)

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The demonstration of the lipotropic activity of choline has led to the testing in experimental animals of its ability to prevent the arterial lipid deposition characteristic of atherosclerosis. Although some observers(1,2) have failed to find any protective action, others(3-6) have claimed that choline administration retards the development of lesions.

In investigating this subject we have administered choline chloride to rabbits by force-feeding gelatin capsules rather than by mixing choline with the food, not only to ensure a known and uniform dosage, but also in order to avoid a possible depression in the food intake of choline-treated animals due to the brackish taste of the chloride. It has previously been shown(7) that caloric restriction with consequent weight loss or decreased rate of weight gain inhibits the development of atherosclerotic lesions.

Methods. Fourteen adult male rabbits of various breeds, kept in individual cages and allowed Purina Rabbit Chow Checkers and water *ad libitum*, were used as experimental

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