of this mixture and following 1 hour adsorption time were overlaid with $hcAE_m$. The same procedure was used in preparation of control plates except that PBS was substituted for the antiserum. In the plaque blocking method bovine embryo kidney cell cultures were infected with 100 PFU/0.3 ml of IBR virus and following 1 hour adsorption were overlaid with agar-$hcAE_m$ containing 2.5% antiserum. Control plates infected with IBR virus received maintenance medium containing 2.5% normal serum or 2.5% PBS. Plaque production was prevented by either method.

Summary and conclusions. Plaques were produced by IBR virus on bovine embryo kidney cells by both Dulbecco's agar-overlay and Postlethwaite's liquid overlay methods. The lower plaque titers obtained when the latter method was used were perhaps due to errors in scoring plaques which were not clearly distinct. The formation of plaques by IBR virus was blocked by IBR hyperimmune serum in both the standard tube neutralization test and by incorporation of antiserum into agar-overlay.

Plaquing of IBR virus on bovine embryo kidney cells provided a more quantitative means by which to study the host-range of this virus and a more precise system for the biological assay of infective IBR nucleic acids which may possibly be obtained from the virus.

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Spontaneous Variations in Pulmonary Venous Pressure in Intact Dogs.* (28245)

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It is well established that the systemic veins play an active role in regulation of the circulation. Previous studies(1,2,3) have shown that the pressure in the systemic veins fluctuates constantly, and these fluctuations may be of great magnitude. These spontaneous fluctuations in pressure reflect changes in volume and tone of the systemic veins. Rheoplethysmographic studies have demonstrated the existence of spontaneous alpha and beta volume deflections in the human digital circulation(4) and that the beta deflections reflect variations in postcapillary venous tone (5). Although there has been a relatively large number of studies on the systemic veins, studies on the pulmonary venous system have been few because of inaccessibility of the pulmonary veins in intact animals. However, such studies are important especially since as much blood flows through the cross-sectional area of the 4 pulmonary veins per unit time as traverses the cross-sectional area of the aorta. Thus, the pulmonary veins probably play an important role not only in control of the pulmonary circulation but also of the systemic circulation. Indeed there is evidence that the pulmonary blood volume and, therefore, the capacity of the pulmonary venous reservoir, influence cardiac output(6).

Recent development(7,8) and improvement

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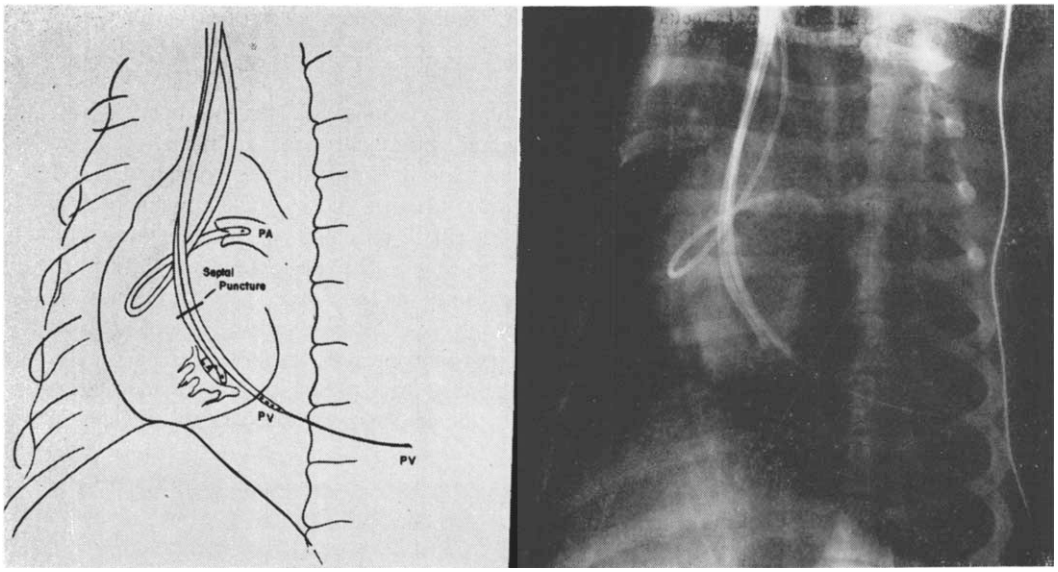

FIG. 1. Position of catheters in experimental preparation used to study spontaneous variations in pressure in pulmonary artery, large and small pulmonary veins and left atrium.

of technics(9) which make it possible to catheterize large and small pulmonary veins in intact dogs permitted a study of the pulmonary venous system under essentially normal physiologic conditions. This report describes spontaneous variations in pulmonary venous pressure in lightly anesthetized intact dogs.

Material and methods. Seven mongrel dogs weighing from 12 to 18 kg were lightly anesthetized with intravenous urethane (1.5 g/kg). The animals were placed supine on a flat fluoroscopic table and an endotracheal tube was inserted. The femoral artery was cannulated with an 18-gauge Cournand indwelling needle. Cardiac catheterization was performed *via* a jugular vein. A red Kifa catheter (external diameter 2.0 mm, internal diameter 1.15 mm) was inserted into the main pulmonary artery and positioned just on the arterial side of the semilunar valves. The left side of the heart was catheterized by puncture of the interatrial septum with an 18-gauge thin-walled Ross needle. Two yellow Kifa catheters (external diameter 2.85 mm, internal diameter 1.50 mm) were passed through the septum on 2 successive punctures. One catheter was placed in the left atrium and the other in an inferior pulmonary vein. A small polyvinyl BD VX020 catheter (external diameter 0.99 mm, internal diameter 0.51 mm) was advanced into a small pulmonary vein through the catheter in the pulmonary vein until it became "wedged." The catheter was then withdrawn until it was out of the wedge position as judged by the pressure tracing. The small polyvinyl catheter was firmly fixed to the large catheter in the pulmonary vein by means of a specially prepared adapter. Thus, any change in position of the catheters must be reflected by a pressure change in both the large and small pulmonary veins and therefore readily detected. Fig. 1 shows the position of the 4 catheters during an experiment. The phlebostatic axis was estimated from fluoroscopic examination of the heart in the anteroposterior and lateral projections. The catheters and Cournand needle were connected by means of polyethylene tubing to Statham strain-gauge transducers (No. P23D), and pressures were recorded with an Electronics for Medicine oscilloscopic recorder.

The mean femoral artery, pulmonary artery, large and small pulmonary vein and left atrial pressures were recorded simultaneously. During the recording of the pressures the experimental preparation was not disturbed. When clotting of blood within a catheter occurred the recording of pressures was discon-

TABLE I. Magnitude of Spontaneous Variations In Pressure Within Pulmonary Circulation.

	$\frac{\text{Range}}{\text{Mean}} \times 100$ (%)	Coeff. of variation* (%)	Absolute variation in pressure (mm H_2O)
Pulmonary artery	2.1	.9	5.2
Small pulmonary vein	19.6	6.2	19.7
Large pulmonary vein	28.6	10.3	6.3
Left atrium	7.2	3.0	1.9

* Coefficient of variation $= \frac{\text{Standard deviation}}{\text{Mean}} \times 100$.

tinued, all catheters were flushed with saline and the zero level of each catheter as well as the position of each catheter was rechecked, following which another set of recordings of spontaneous variations in pressure was obtained. A total of 32 sets of continuous tracings was recorded on the 7 dogs, varying in duration from 3 to 10 minutes (average 6.2 minutes).

Anatomical studies. Anatomical dissections showed that the catheter in the small pulmonary vein was well within the parenchyma of the lung. These veins varied from 1.5 to 2.0 mm in diameter.

Analysis of records. Because of the wide fluctuations in level of the baseline of the pressure tracings secondary to respiratory movement a uniform method for calculating the pressure which minimized this effect had to be used. Accordingly the pressures were measured in each vessel and the left atrium at the peak of each respiratory deflection wave, *i.e.*, at the end of expiration.

Results. The results are summarized in Fig. 2 and 3 and Table I.

Pulmonary artery. Slow rhythmic fluctuations in the mean pulmonary artery pressure of small amplitude were seen in all animals which were best appreciated in the longer records. The fluctuations occurred at a frequency of about one every 2 minutes and were only a few millimeters of H_2O pressure in magnitude. The range of variation in mean pulmonary artery pressure was only about 2%. Other than these small, slow rhythmic oscillations there tended to be little variation in mean pulmonary artery blood pressure, the coefficient of variation for all the experiments being 0.9% (Table I).

Small pulmonary vein. The greatest absolute variations in pressure occurred in the small pulmonary veins, mean variation for all experiments being 19.7 mm of H_2O. However, because of the higher mean pressure in the small, as compared to the large pulmonary veins, the coefficient of variation was greater in the large (28.6%) than in the small pulmonary veins (19.6%) (Table I). Spontaneous fluctuations in the small pulmonary vein pressure showed no relationship to the pressure variation in the other pulmon-

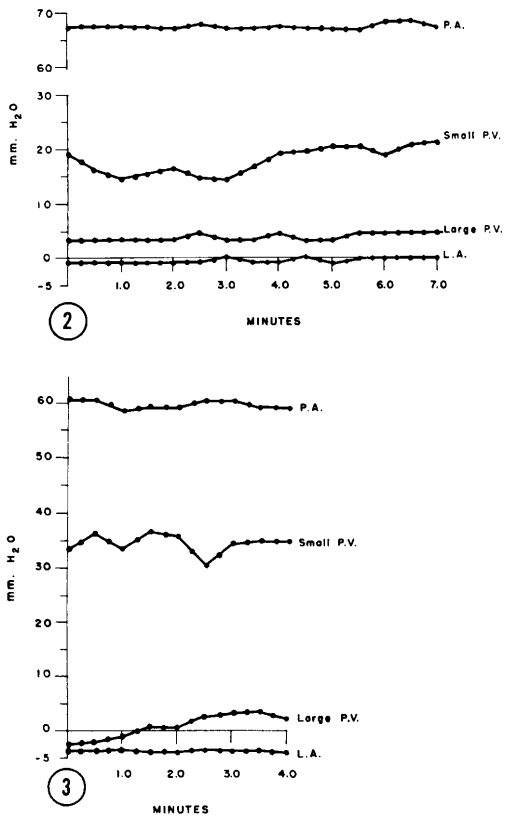

FIG. 2. Spontaneous variations in pressure in pulmonary artery, small and large pulmonary veins and left atrium. Pressure in small pulmonary vein varied independently of pressure changes in the other pulmonary vessels and left atrium. Pressure changes in large pulmonary vein and left atrium were frequently discordant.

FIG. 3. In this recording pressure in large pulmonary vein also changed independently of pressure in left atrium and small pulmonary vein, but magnitude of pressure variation was much greater than shown in Fig. 2. Pressure in pulmonary vessel and left atrium were rarely at a constant level.

ary vessels. Furthermore, the variations in pressure were not rhythmical.

Large pulmonary vein. The pressure within the large pulmonary veins varied over a range of 6.3 mm of H_2O. Variations in pressure within the large pulmonary veins tended to vary with pressure changes in the left atrium rather than with those in the small pulmonary vein (Fig. 2). However, at times the pressure within the large pulmonary vein varied independently of changes in pressure within the left atrium or the small pulmonary vein (Fig. 3).

Left atrium. The pressure within the left atrium remained remarkably constant in all experiments, average variation in pressure being 1.9 mm of H_2O. Although the large pulmonary vein pressure at times varied independently of left atrial pressure a change in left atrial pressure was always associated with a similar change in pressure in the large pulmonary veins.

Femoral artery. Spontaneous rhythmic fluctuations in mean systemic arterial blood pressure occurred in all the animals studied. These fluctuations corresponded to the vasomotor waves (Mayer waves) well known to occur in the systemic arterial circulation(10). The fluctuations showed no relationship to any of the spontaneous variations in pressure observed in the pulmonary circulation.

Pressure gradient between pulmonary veins and left atrium. The mean pressure gradient between the small pulmonary vein and the left atrium was 93.8 mm of H_2O (6.9 mm of Hg) whereas that between the large pulmonary vein and the left atrium was 24.5 mm of H_2O (1.8 mm of Hg). The magnitude of the pressure gradient between the small pulmonary vein and left atrium depended upon the position of the catheter in the small pulmonary vein. The nearer the catheter was placed to the pulmonary "wedge" the smaller the vein and the higher the pressure and therefore the greater the pressure gradient.

The pressure gradient between the large pulmonary veins and the left atrium usually remained quite constant. However, changes in the pressure gradient as great as 3 to 5 mm of H_2O were not infrequent. Larger fluctuations in the gradient although unusual also occurred (Fig. 3).

Discussion. These studies demonstrate that spontaneous fluctuations in pressure, independent of respiratory movement, occur in the pulmonary artery and pulmonary veins. Although pneumographic pressures were not recorded during these experiments variations in depth of respiration could not have produced the fluctuations in blood pressure observed because the changes in pressure were so frequently discordant. For example, it was not unusual for the pressure in one vessel to rise while that in another vessel was falling or not changing. Variations in depth of respiration should have resulted in concordant increases or decreases in blood pressure.

Spontaneous fluctuations in pulmonary artery and left atrial pressures were extremely small and therefore were expressed in H_2O rather than Hg pressure. However, spontaneous fluctuations in pulmonary venous pressure were relatively great. The complete independence of the small pulmonary vein pressure, and at times of the large pulmonary vein pressure, from pressure changes in other blood vessels was remarkable, and in this respect was quite similar to the systemic veins. Stead and Wallace(3) catheterized a small pulmonary vein of the hand and a large vein in the ipsilateral forearm and observed large spontaneous fluctuations in pressure in the small vein without corresponding changes in pressure in the large vein. We have observed similar spontaneous changes in pressure in a large and small vein of the forearm.

The nature and importance of the spontaneous variations in pulmonary venous pressure is unknown. However, it is likely that pressure variations reflect changes in pulmonary venous blood volume. It has been shown that the pulmonary veins like the systemic veins constitute a distensible reservoir for blood(11). Changes in volume of the reservoir have generally been considered to be passively dependent upon the balance between right ventricular inflow volume and left ventricular outflow volume and the state of bronchopulmonary circulation. However, such an interpretation would be inconsistent with

what is known concerning the physiology of the veins in other parts of the circulation. Although differences in right and left ventricular output and bronchopulmonary circulation can modify pulmonary blood volume, it is also to be expected that the vessels of the pulmonary circulation should undergo spontaneous volume changes.

Spontaneous fluctuations in pressure have been observed in the intact forearm veins of man which are temporally related to the alpha and beta volume deflections observed in the digits with the rheoplethysmograph. Indeed every organ which has been studied plethysmographically has shown a pattern comparable to the alpha and beta volume deflections of the digit(12). It is, therefore, difficult to understand why the lung should not behave in a similar manner. Local regulation of the size of the pulmonary venous reservoir would serve to adjust rapidly the volume of the reservoir in response to sudden changes in position during the lag period required for the more complex regulation of the circulation by means of integrated neurogenic reflexes. Spontaneous fluctuations in pulmonary venous pressure may well represent spontaneous adjustments in volume of the pulmonary venous reservoir mediated through local receptors within the veins.

It is recognized that changes in total pulmonary blood flow alter pulmonary venous pressure(13). However, that the spontaneous pressure changes observed were discordant among different veins would tend to exclude the possibility that they were merely secondary to changes in rate of total pulmonary blood flow.

The fluctuations in magnitude of the pressure gradient between the large pulmonary vein and the left atrium are of interest. In previous studies from this laboratory it was shown that a sleeve of atrial myocardium encloses the terminal portions of each of the 4 pulmonary veins and it was suggested that this sleeve of myocardium may serve as a valve to prevent regurgitation of blood into the pulmonary veins(14). Recently, in a study of the volume-pressure relationships within the left atrium and pulmonary veins, Little(15) suggested that at low left atrial pressures there was closure of the pulmonary veins at their junction with the left atrium. The fluctuations in pressure gradient between the large pulmonary veins and the left atrium found in the present studies indicate that the large pulmonary veins and left atrium are not always in free communication.

The spontaneous fluctuations in pulmonary venous pressure may also reflect variation in smooth muscle tone in walls of these vessels. These variations in tone may in turn help to regulate the volume of blood flow through the lungs and into the left side of the heart. A "throttle" action on the part of the pulmonary veins which influences the pulmonary blood flow and rate of venous return to the left ventricle could be of considerable importance in regulation of the circulation. Whether or not these fluctuations are concerned with local circulatory phenomena in the lungs as described previously for the spontaneous alpha and beta deflections of the digits(5) is not known. There is need to study the spontaneous variations in tone of the pulmonary vessels, in health and in disease.

Summary. Continuous and simultaneous pressures were recorded from the pulmonary artery, small pulmonary vein (1.5-2.0 mm in diameter), large pulmonary vein and left atrium in 7 intact dogs lightly anesthetized with urethane. Pressures within the pulmonary artery and left atrium remained relatively constant whereas pressure in the small pulmonary vein varied widely. Pressure in the large pulmonary vein fluctuated over a narrower range than did the pressure in the small pulmonary veins. At times the pressure in the large pulmonary vein changed without a corresponding change in left atrial pressure, It is suggested that the pulmonary venous blood reservoir behaves in a manner similar to the systemic venous blood reservoir and that pressure variations reflect spontaneous adjustments in volume of the reservoir. The findings also support the concept of a "throttle valve" action of the pulmonary veins.

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Effect of Several Drugs and Chemicals on Hepatic Glucuronide Formation in Newborn Rats.* (28246)

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The administration of various drugs to rats and guinea pigs increases the activity *in vitro* of several hepatic microsomal enzymes which metabolize drugs(1-10) and, *in vivo,* the duration of drug action is decreased by pretreatment with these same agents(7,8). In addition, some drugs increase the activity of uridine diphosphate glucose (UDPG) dehydrogenase which is not a microsomal enzyme(11, 12). Although the mechanism of these effects is uncertain, several studies suggest that the enzyme synthesis is induced(1,4,12-14).

The transient unconjugated hyperbilirubinemia of newborn infants is currently believed to result from a normally occurring delayed development of the hepatic glucuronide conjugating system(15,16). Although hepatic UDPG dehydrogenase activity is reduced in newborns as compared with adults, the major limitation in glucuronide formation in neonates is in glucuronyl transferase. This microsomal enzyme catalyzes the transfer of glucuronic acid from uridine diphosphate glucuronic acid (UDPGA) to bilirubin forming bilirubin glucuronide which is subsequently excreted in the bile.

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Inscoe and Axelrod(17) treated neonatal rats and guinea pigs with 3,4 benzpyrene and observed an increase in hepatic glucuronyl transferase activity *in vitro.* These observations prompted a study of the effect of various drugs and chemicals on hepatic glucuronide formation in newborn rats and on the course of hyperbilirubinemia in human neonates.

Methods. Wistar rats in late pregnancy were obtained from the Camm Research Institute, Inc., Wayne, N. J. The estimated time of parturition is accurate to within 12 hours. Pregnant rats were fed mouse breeder chow up to the time of sacrifice and newborn rats were nursed by their mothers.

3,4 Benzpyrene; 1-(4-chloro-benzhydryl)-4-methylpiperazine dihydrochloride (chlorcyclizine); 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline (chloroquine), and 8-(4 - diethylamino - 1 - methylbutylamino) - 6-methoxy quinoline (pamaquine) were separately administered to pregnant and newborn rats in various doses.

O-aminophenol (OAP) glucuronide and direct-reacting bilirubin formation were estimated in liver homogenates with the addition of optimal amounts of UDPGA(18,19).