homogenous venous sample for the entire heart since determination of the steady-state levels of lactate showed the apices of the myocardium to contain almost double the atrial concentration. The implication of such a distribution raises serious questions on attempting to assess lactate metabolism of the heart from levels present in coronary sinus blood.

Summary. The concept that blood lactate is in equilibrium with myocardial concentrations of this substrate could not be demonstrated in the anesthetized dog. A factor questioning the existence of an equilibrium was the distribution of lactate found in the walls of the heart. Levels in right and left atria were markedly different from those found in the base, midportion and apex of the right and left ventricles. Although administration of sodium lactate by vein raised arterial lactate almost 6 times control, right and left ventricular muscle concentrations remained unchanged. The linear relationship observed between the duration of myocardial anoxia and lactate production by cardiac muscle made possible the calculation of the *in vivo* myocardial lactate level, a value significantly higher than the level present in arterial blood. The entry of lactate into the myocardial cell may therefore be governed by a mechanism of active transport rather than simple diffusion.

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Effect of Chronic Hypoxia on the Pulmonary Circulation of Cats.* (30069)

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In the cat, acute hypoxia causes an increase in pressure in the pulmonary artery (1-6). The increase is due to a constriction of pulmonary vessels caused by a local but unknown effect of hypoxia on the pulmonary vessels. This study reports the effect of chronic hypoxia on the pulmonary circulation of the cat.

Methods. Nitrogen was added to room air and the mixture was introduced into a 15-cubic-foot box at 15 to 20 L per minute. The oxygen content of the atmosphere in the box was checked at least once weekly with a Pauling oxygen meter (accuracy, within 1%) and ranged from 9 to 11%; carbon dioxide content was negligible. Temperature in the box was maintained at 72°F.

Cats varying in age from 2 weeks to 2 years were kept in the box for 3 weeks to 10 months; the chamber was opened daily for 5 to 10 minutes for cleaning and feeding.

The cats were removed from the box at intervals, exposed to room air for ½ to 1 hour, and then anesthetized with sodium pentobarbital (20 mg/kg). A catheter, intro-

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duced by percutaneous puncture of the jugular vein, was passed into the right atrium and the right ventricle; pressures were measured by a strain-gauge transducer. The zero reference point was midway between the upper and lower aspect of the cat's chest. The catheter-manometer-galvanometer assembly had a uniform response to 8 cps(7). The pressure measurements were made while the cats were breathing air, 10% oxygen, and 99.6% oxygen, successively. Blood was taken from the right atrium or right ventricle for determination of hematocrit value. In 2 cats, cardiac output was measured by the indicator dilution technic; indocyanine green (Cardio-Green) dye was injected into the right ventricle, and the resultant dye dilution curve was recorded by a Waters densitometer connected to a catheter in the femoral artery. The blood withdrawn during the recording of a dilution curve (5 to 7 ml) was reinfused to the animal after each curve had been recorded.

Similar studies were carried out on littermates maintained in a normal room atmosphere. Necropsy was done on all animals that died or were killed during the study. Tissue blocks were taken from all lobes of both lungs of the normal animals and from those exposed to the 10% oxygen environment. At least 2 histologic sections were prepared from each block, one being stained with hematoxylin and eosin and the other with Lawson's elastic stain and van Gieson counterstain. Specimens from one lobe of each of 3 of the cats (2 from the hypoxic group) were examined by electron microscopy.

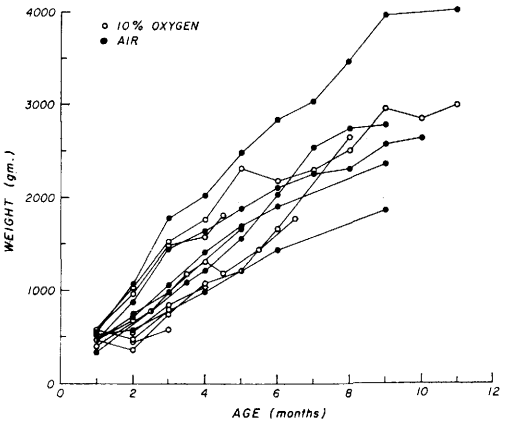

FIG. 1. Growth curves of kittens raised in 10% oxygen (open circles) and littermates raised in a normal atmosphere (closed circles).

Results. Of 17 animals placed in the box, 5 died suddenly of an acute respiratory infection. The remainder thrived, maintaining growth curves comparable to those of littermates raised in a normal atmosphere (Fig. 1).

Two kittens were placed in the box when they were 2 weeks old, 4 at 1 month of age, and 2 at 2 months of age (Table I). After 1 to 4 months of exposure to the low oxygen environment, the average hematocrit value was 52% and the average right ventricular systolic pressure when breathing room air was 59 mm of mercury. Littermates raised in a normal atmosphere had an average

TABLE I. Effect of Chronic Hypoxia on Right Ventricular Systolic Pressures in Young Cats.

Cat	Age at entry into chamber (mo)	Duration of exposure to 10% oxygen (mo)	After exposure to hypoxia: Wt (kg)	Hemat value (%)	R.V. systolic press (mm Hg): Air	10% O_2	99.6% O_2
1	½	1	—	43	84	90	86
2	½	3½	3.6	58	80	92	72
3	1	2½	1.8	47	75	87	67
4	1	4	2.3	53	40	45	35
		8	2.9	59	45	50	40
		9	3.0	41	32	47	30
		10	2.9	50	27	35	22
5	1	3	1.3	55	48	—	—
6	1	3	1.1	56	58	72	55
		6	2.1	54	47	72	45
		7	2.6	51	40	94	40
		10½	—	65	62	—	—
7	2	1	0.6	48	46	55	35
8	2	1	0.9	57	37	44	33

TABLE II. Control Values and Effect of Short-Term Hypoxia on Right Ventricular Pressures in Cats.*

Cat	Age at time of study (mo)	Duration of exposure to 10% oxygen (mo)	Wt (kg)	Hemat value (%)	R.V. systolic press (mm Hg) Air	10% O_2	99.6% O_2
9†	4	None	1.1	27	22	38	18
	5	"	1.2	28	18	50	18
	6	"	1.4	24	18	30	18
	7	"	1.7	25	18	41	18
	8	¾	1.9	56	29	48	25
10‡	9	None	2.8	20	20	27	15
	10	"	2.8	30	18	28	15
	12	¾	2.6	47	20	25	20
11§	3	None	0.9	28	14	28	13
	4¼	¾	1.6	42	28	34	25
	8	None since 4¼ mo old	2.0	30	22	—	—
12	25	1	—	58	30	—	22
	27½	3½	3.6	56	38	50	35

* Cats not exposed to hypoxia until they were 4¼ months old or older.
† Littermate of cat 6 (Table 1).
‡ " " " 4 (Table 1).
§ " " " 7 (Table 1).

hematocrit value of 26% and a right ventricular pressure of 17 mm (Table II). There was no difference in right atrial or right ventricular end-diastolic pressure between the two groups. The kittens placed in the chamber at 2 weeks of age had higher right ventricular systolic pressures than did those started later in life (Table I).

When animals raised in either an oxygen-deficient or a normal atmosphere breathed 10% oxygen instead of room air, there was an increase in right ventricular systolic pressure. In the former, the pressure increased from an average of 59 to 69 mm; in the latter, from 17 to 32 mm. When 99.6% oxygen was breathed, the average pressure in the animals raised in the oxygen-deficient atmosphere decreased to 55 mm while that of the control cats decreased to 15 (Tables I and II, Fig. 2 and 3). Thus the cats raised in an oxygen-deficient atmosphere had a higher right ventricular systolic pressure when breathing 99.6% oxygen than did the control cats when breathing 10% oxygen.

Because of the technical difficulty involved, the pulmonary artery was entered in only one of the cats with increased ventricular pressure (cat 4, Table I); the systolic pressure in the pulmonary artery, 40 mm, was identical to that in the right ventricle. In the animals that died during the studies, no obstruction of the outflow tract of the right ventricle was found at necropsy. Therefore, it is very likely that, in all of the cats, the systolic pressure in the pulmonary artery was equal to the systolic pressure in the right ventricle. In all of the cats, including one 3 weeks of age, the ductus arteriosus was anatomically closed.

Four animals (Table II) were raised in a normal atmosphere and then were placed in the oxygen-deficient environment at 3½ to 24 months of age; they were kept under the hypoxic condition until their hematocrit values increased to levels comparable to those in the animals placed in the box at a younger age (52%). The hematocrit values increased to an average of 51% in 3 to 4 weeks. At that time, the average right ventricular systolic pressure when breathing room air, 27 mm, was considerably below that of the group exposed to oxygen deficiency at an earlier age.

One cat (cat 6, Table I), raised in the oxygen-deficient environment since one month old, had a hematocrit value of 51% and a systolic pressure of 40 mm at 8 months of age when breathing room air and 94 mm when breathing 10% oxygen. A littermate (cat 9, Table II), placed in the oxygen-defi-

cient environment at 7¼ months and studied 3 weeks later, had a hematocrit value of 56% and a systolic pressure of 29 mm when breathing room air and 48 mm when breathing 10% oxygen. Thus, in cats of similar size and hematocrit value, there was a difference in systolic pressure in the right ventricle.

Additional studies were performed on cat 6 after it had been in the oxygen-deficient atmosphere for 7 months (when the cat was 8 months old) (Table III). When the cat was breathing 99.6% oxygen, simultaneous right ventricular and aortic systolic pressures were 40 and 126 mm, respectively; the hematocrit value was 51%, and the cardiac out-

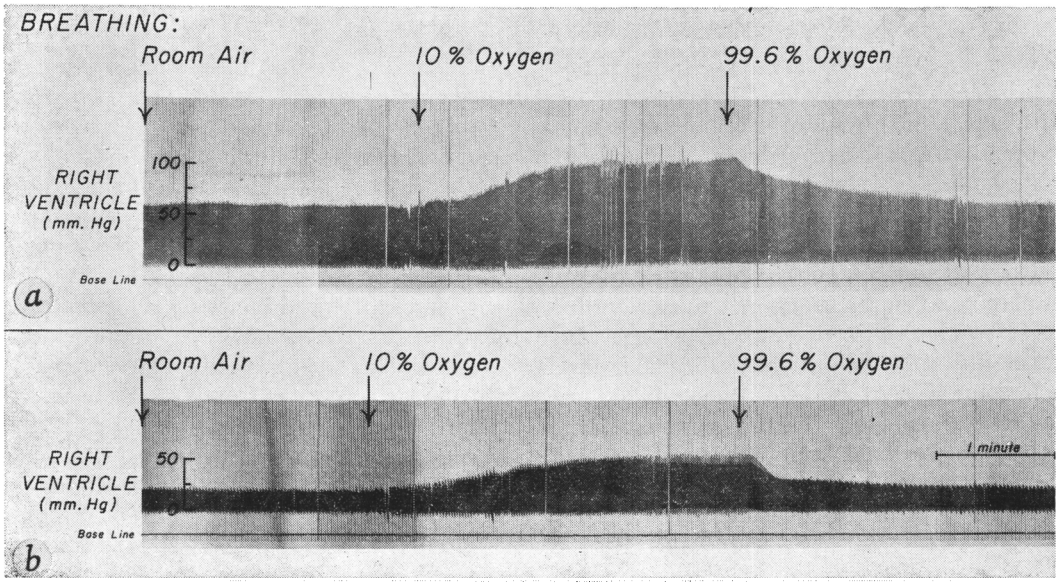

FIG. 2. Right ventricular pressure records: *a*, 4-mo-old cat raised in 10% oxygen from 1 mo of age and *b*, littermate raised in room air. The pressure increased in both animals when they breathed 10% oxygen and decreased with 99.6% oxygen.

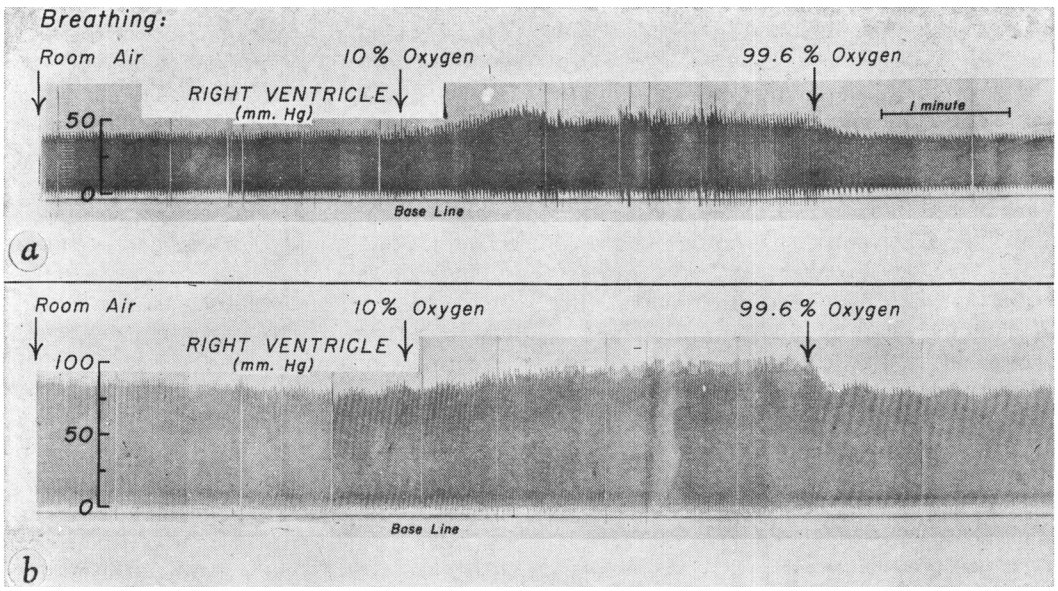

FIG. 3. Right ventricular pressure records of *a*, an adult cat exposed to 10% oxygen for 3½ mo and *b*, its 3½-mo-old kitten exposed to 10% oxygen from 2 wk of age.

TABLE III. Additional Hemodynamic Studies.*

Dextran exchanged (ml)	Hemat value (%)	Pressure (mm Hg)† Air R.V.	Air Aorta	10% O_2 R.V.	10% O_2 Aorta	99.6% O_2 R.V.	99.6% O_2 Aorta	Cardiac output (ml/min) Air	10% O_2	99.6% O_2
0	51	40/0	158/119	94/0	176/128	40/0	126/95	275	290	300
30	35	—	—	—	—	54/0	135/100	—	—	250
60	19	—	—	—	—	58/0	172/100	—	—	310

* Cat was 8 months old and had been in an oxygen-deficient atmosphere since it was 1 month old.
† R.V. = right ventricle. Pressures shown as systolic/diastolic.

put was 300 ml per minute. An exchange transfusion was carried out to replace blood with equal quantities of a solution of high molecular-weight dextran; after exchange of 60 ml, the hematocrit value decreased to 19% with no change in right ventricular pressure or cardiac output. Since the viscosity of the dextran solution is greater than that of plasma, when the hematocrit value returned to 51%, another study was carried out with equal quantities of isotonic saline and dextran solution used as the exchange fluid. The results were similar. These experiments suggest that the right ventricular hypertension due to chronic hypoxia is not caused primarily by the increased hematocrit value.

The increase in right ventricular systolic pressure in cat 6 was not due to an increased cardiac output. When the cat was breathing room air, the cardiac output was 275 ml per minute (Table III). A control animal of the same weight had a similar cardiac output with a hematocrit value of 30% and a right ventricular systolic pressure of 18 mm. These outputs are within the limits described by Cross and co-workers(8) and Baxter and co-workers(9) for normal cats. When cat 6 breathed 10% oxygen instead of air, the right ventricular pressure increased to 94 mm with only a 6% increase in cardiac output. In the control animal, the pressure increased to 30 mm with an 8% increase in cardiac output.

When cat 6 was 12 months of age, it was transfused with plasma from 2 other cats until the hematocrit value decreased to 15%. When the cat was breathing room air, the cardiac output was more than double the value on the previous study; this is consistent with the effect of increased blood volume and decreased hematocrit value reported by other investigators(10,11). When the cat was breathing 10% oxygen, there was an increase in the right ventricular systolic pressure from 60 to 105 mm. Cardiac output showed a modest decrease. Following this, the animal breathed 99.6% oxygen; ventricular pressure decreased to 60 mm and cardiac output returned to the value noted when the animal was breathing air.

Specimens from the lungs of 10 of the cats raised in the oxygen-deficient environment were examined histologically and compared with similar specimens from 7 normal cats of similar age. The lungs from the latter group showed the typical small muscular pulmonary arteries and arterioles with relatively thick muscular media(12-15). In 8 cats of the former group, the external diameter, medial and intimal thicknesses, and wall-to-lumen ratio of the precapillary vessels did not differ from normal despite the fact that 2 of these cats (No. 2 and 3, Table I) had right ventricular systolic pressures of 80 and 75 mm of mercury when breathing air. In 2 of the 10 cats No. 5, Table I, and a 3-month-old cat which did not have a hemodynamic study) there was a slight increase in medial thickness.

The electron microscopic studies did not reveal any differences in the alveolar capillary walls on comparison of the normal to the hypoxic cats.

Discussion. Right ventricular and pulmonary hypertension develops in cats subjected to chronic exposure to an oxygen-deficient environment at an early age. The extent of the increase in pressure seems to depend on the age of the cat at initial exposure, since cats placed in this environment at 2 weeks of age developed higher pressures than did cats whose exposure started when they were older. No kittens have actually been born in the oxygen-deficient environment; the kittens of 2 cats placed in the box in late pregnancy

were stillborn. The hypertension is not primarily a consequence of the increased hematocrit value since cats placed in an oxygen-deficient atmosphere at 3½ months of age or later had the same increase in hematocrit value as the younger cats but without the same increase in pressure; reduction of the hematocrit value to normal by exchange transfusion in the hypertensive cat did not lead to a reduction in pressure. However, other variables that might affect blood flow through the lungs, such as blood volume and shape of erythrocytes, were not studied and cannot be excluded as contributing factors. Pulmonary hypertension develops in some Hereford calves when they are at altitudes greater than 10,000 feet; this is due to constriction of pulmonary vessels since cardiac output, blood volume, and hematocrit value show little, if any, change(16-18).

Other studies have shown that, in hypoxia, closure of the ductus arteriosus may be delayed(19). However, in the present experiments the ductus was closed at the time that pulmonary hypertension was present and, therefore, increased flow from the aorta to the pulmonary artery could not explain the hypertension. The fact that the right ventricular systolic pressure did not decrease to normal when the cats with pulmonary hypertension breathed oxygen instead of air means that, in the absence of any hypoxic stimulus, there probably is a residual increase in resistance to blood flow through the pulmonary vessels. When breathing 10% oxygen instead of air, cats made hypertensive by prolonged exposure to the oxygen-deficient environment from an early age show a further increase in pressure which, like that of the normal cat, is not due to an increase in pulmonary flow. Since left atrial and pulmonary vein pressures were not measured, the cause of the pulmonary hypertension cannot be stated with certainty; it is most likely due to constriction of vessels somewhere in the lung.

The morphologic features of the pulmonary vessels of the cats subjected to chronic hypoxia did not differ significantly from those seen in the normal animals. Thus, the pulmonary hypertension cannot be easily explained by anatomic changes in the pulmonary vessels.

Dill(20) stated that cats rarely survive at an altitude of over 13,000 feet and Reeves and co-workers(21) reported recently that cats living at an altitude of 14,150 feet failed to thrive, did not develop pulmonary hypertension, and died in 1 to 2 months. The animals in the present study were exposed to an atmosphere containing a percentage of oxygen comparable to that at about 20,000 feet, but at a barometric pressure of about 735 mm of mercury. However, the partial pressure of inspired oxygen, and not the total barometric pressure, is responsible for the effects of hypoxia on pulmonary circulation (22). Thus, the death of the cats in the previous studies may have been related to the inclement conditions present at high altitudes and not to chronic hypoxia.

Summary. Cats subjected to chronic exposure to an oxygen-deficient environment (10%) at an early age thrive and develop an increased systolic pressure in the right ventricle (average 69 mm Hg compared to 32 mm Hg in littermates subjected to acute exposure). The pressure decreases when the cats breathe normal air (average pressure, 59 mm compared to 17 in littermates) but does not decrease to normal when 99.6% oxygen is breathed (average pressure, 55 mm compared to 15 in littermates). The average hematocrit value was 52 compared to 26% in controls. The increase in pressure is not a consequence of the increased hematocrit value, change in cardiac output, or delay in closure of the ductus arteriosus. Evidence is presented that the same systolic pressure exists in the pulmonary artery as in the right ventricle and that the most likely cause of the increased ventricular pressure is an increased resistance to blood flow through the pulmonary vessels. There was no evidence of anatomic changes in the pulmonary vessels.

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Restoration of Antibody Producing Capacity in Bursectomized Chickens by Bursal Grafts in Millipore® Chambers.* (30070)

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Recent studies have established that the bursa of Fabricius plays a major role in antibody production in birds(1). Neonatally bursectomized chickens fail to respond to antigenic challenge with an increase in number of plasma-cellular elements(2) and exhibit a striking suppression of antibody formation, whereas the delayed responses remain unchanged(3). The immunologic deficiency caused by removal of bursa could be partially restored by treating bursaless birds with a saline extract of bursa(4) or by grafting bursectomized chickens with bursa from newly hatched or 8-week-old chickens(2). These experimental findings suggest that the bursa may exert a hormone-like function in the development of immunological responsiveness in birds. To explore this hypothesis further, a study was made of the effect of bursa grafts in cell-impermeable millipore® chambers on antibody production to human erythrocytes in bursectomized chickens.

White Rockland chickens were surgically bursectomized under ether anesthesia within 24 hours after hatching. At the age of 8 weeks one group of bursectomized chickens had implanted a millipore chamber containing bursa from a 4-day-old chicken. A second group of bursaless birds was implanted with an empty millipore chamber, and a third group of non-operated birds served as controls. The chambers were made by cementing 2 discs of nylon supported millipore filter having a pore size of 0.45 μ (Millipore Filter Co., Bedford, Mass.) to lucite rings (inner diameter 17 mm, height 3 mm). The bursae were evaginated prior to placement in the chamber, which was thereafter filled with

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