Elevation of the pulmonary arterial pressure is known to occur during hypoxia in a number of mammalian species. The mechanisms involved in the production of this hypertension are, however, not clearly understood. Most previous investigations have been concerned with the effect of short periods of severe hypoxia upon the pulmonary circulation. The effects of mild, prolonged hypoxia are less well documented. Rotta et al. reported an increase in the pulmonary arterial pressure and resistance, polycythemia, and hypervolemia in both temporary and permanent human residents of Moraeocha, Peru (altitude 14,900 feet). They suggested that the pulmonary hypertension might relate to the observed increase in hematocrit and blood volume rather than to a direct effect of hypoxia on the pulmonary vasculature.

It has been known for many years that a small percentage of cattle residing at high altitude develops right heart failure. In 1915, Glover and Newsom described a syndrome of right heart failure with venous distention, weakness, dyspnea on exertion, diarrhea, and edema of the dependent portions of the neck and thorax occurring in cattle pastured in the high mountain valleys of Colorado. Hypertrophy and dilatation of the right ventricle, passive congestion of the liver, hydrothorax, and ascites were found at necropsy. The edema present in the pectoral region gave rise to the name "brisket disease," although the term "high mountain disease" seems more explicit. In 1956, Piersen and Jensen hypothesized that "atmospheric hypoxia causes pulmonary changes which lead to increased resistance to circulation through the lungs and failure of the right ventricle." Their postulation has since received support by the constant finding in this disease of right ventricular hypertrophy and an elevated pulmonary arterial pressure.

Based upon the hypothesis that chronic hypoxia is a causative factor in high mountain disease, the following experiment was designed to study the effect of a high altitude environment upon the pulmonary circulation in normal cattle.

**Methods**

Twenty yearling Hereford steers, approximately 300 Kg, in body weight and of uniform breeding, were obtained from a single ranch in eastern Colorado at an altitude of 3,600 feet. The animals were transported to Fort Collins, Colorado, elevation 5,000 feet, in May, 1955, and randomized by weight into two groups of 10 animals each. One group served as the "controls" and was maintained at an elevation of 5,000 feet throughout the experiment. The second group underwent initial cardiac catheterization at 5,000 feet in June. On this occasion only, these animals were studied after premedication with chlorpromazine, before the undesirable effects of this drug were fully appreciated. Although the drug caused abnormal fluctuations in a number of determinations, the data obtained on vascular pressures were not significantly altered and are included in the results for the June measurements. These steers were then moved to a cattle ranch near Fairplay, Colorado, altitude 10,000 feet, where subsequent hemodynamic measurements were made in August, October, and December, 1956. In December, the effects of the 100 per cent oxygen inhalation were observed in two of these animals. In addition, a heifer with "high mountain disease" was catheterized at 10,000 feet and on three subsequent occasions after being moved to 5,000 feet. These pressure measurements are relevant, even though...
TABLE 1
Mean Vascular Pressures, Cardiac Output, and A-V Oxygen Difference

<table>
<thead>
<tr>
<th>Month</th>
<th>Group</th>
<th>Pulmonary arterial pressure (mm. Hg)</th>
<th>&quot;Wedge&quot; pressure (mm. Hg)</th>
<th>Right atrial pressure (mm. Hg)</th>
<th>Cardiac output (L/min.)</th>
<th>A-V oxygen difference (cc./L.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>June</td>
<td>C</td>
<td>28 ± 4.5</td>
<td>9 ± 5.4</td>
<td>6 ± 2.6</td>
<td>36 ± 11</td>
<td>48 ± 8</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>27 ± 5.9</td>
<td>10 ± 2.1</td>
<td>5 ± 1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>26 ± 1.0</td>
<td>7 ± 3.3</td>
<td>6 ± 5.7</td>
<td>33 ± 10.4</td>
<td>54 ± 10</td>
</tr>
<tr>
<td>August</td>
<td>C</td>
<td>28 ± 4.3</td>
<td>13 ± 3.3</td>
<td>9 ± 7.1</td>
<td>32 ± 4.5</td>
<td>58 ± 7</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>36 ± 4.1**</td>
<td>14 ± 3.5</td>
<td>6 ± 3.7</td>
<td>31 ± 8.2</td>
<td>47 ± 12</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>62 ± 13.0†††§§§§ 17 ± 7.1</td>
<td>9 ± 7.1</td>
<td>27 ± 9.0†††§§§</td>
<td>61 ± 13</td>
<td></td>
</tr>
<tr>
<td>October</td>
<td>C</td>
<td>25 ± 4.8</td>
<td>13 ± 3.2</td>
<td>7 ± 4.5</td>
<td>31 ± 9.1</td>
<td>59 ± 10</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>30 ± 2.0***</td>
<td>12 ± 5.9</td>
<td>6 ± 4.3</td>
<td>32 ± 7.2</td>
<td>56 ± 17</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>63 ± 19.2†††§§§§ 20 ± 4.9</td>
<td>27 ± 7.3</td>
<td>57 ± 9.0†††§§§§</td>
<td>61 ± 13</td>
<td></td>
</tr>
<tr>
<td>December</td>
<td>C</td>
<td>27 ± 4.4</td>
<td>12 ± 4.7</td>
<td>4 ± 2.3</td>
<td>33 ± 8.4</td>
<td>62 ± 13</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>45 ± 4.7***</td>
<td>14 ± 5.2</td>
<td>8 ± 6.4*</td>
<td>36 ± 8.4</td>
<td>62 ± 16</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>90 ± 55.0***</td>
<td>15 ± 5.7</td>
<td>21 ± 16.1**</td>
<td>26 ± 10.1</td>
<td>75 ± 11</td>
</tr>
</tbody>
</table>

Group C = Controls (10).
Group M = Moderate hypertension (6).
Group S = Severe hypertension (4).
* = Comparing C versus M.
† = Comparing C versus S.
§ = Comparing M versus S.
One superscript = \( P < 0.05 \).
Two superscripts = \( P < 0.01 \).
Three superscripts = \( P < 0.001 \).

The animal was not part of the experimental group.

Feeding and management of the animals at high altitude were essentially the same as for the control group. Their activity was restricted by confining them to a corral; they were fed identical rations of alfalfa hay and concentrate pellets grown and prepared at low altitude. Supplemental salt was offered. At high altitude, the source of water was different, the environmental temperatures were lower, and the animals gained weight more slowly. However, these variables were probably of minor importance compared with the lower atmospheric pressure to which the cattle were exposed at 10,000 feet.

The cardiac catheterization procedure including the methods used to measure right heart pressures, oxygen uptake, cardiac output, plasma volume, hemoglobin, hematocrit, oxygen saturation, and carbon dioxide content are reported elsewhere. At the termination of the experiment, the animals were sacrificed and examined for gross pathological changes. The hearts were divided into ventricular components, weighed, and the ratio of each ventricular component to the total ventricular weight was obtained.

Results

Eighty separate cardiac catheterization studies were carried out during the course of the experiment. For each class or group of data the results are presented in tabular form, giving the group means, standard deviation, and statistical comparisons.

CARDIOVASCULAR PRESSURES

Pulmonary Artery Pressure

Beginning in August, all 10 steers at the altitude of 10,000 feet showed elevated pulmonary arterial pressures when compared to either the low altitude "controls" or to their own initial measurements (table 1). Due to individual differences in pressure elevation, the animals were divided into two subgroups.

Subgroup M: Moderate Pulmonary Hypertension (Animals 4, 5, 12, 13, 15, 16)

The control value for the mean pulmonary arterial pressure for these six steers was 27 mm. Hg. This mean pressure had increased to 36 mm. Hg after six weeks and continued to rise to 45 mm. Hg at the end of six months. The rate of pressure increase was similar for all six animals as indicated by the small standard deviation at each observation period.

Subgroup S: Severe Pulmonary Hypertension (Animals 2, 3, 17, 19)

These animals also had a normal control mean pulmonary arterial pressure of 26 mm. Hg. However, at the time of each subsequent study at high altitude, this pressure was
TABLE 2

<table>
<thead>
<tr>
<th>Date</th>
<th>Pulmonary arterial pressure (mm. Hg)</th>
<th>Right atrial pressure (mm. Hg)</th>
<th>&quot;Wedge&quot;</th>
<th>Cardiac output (L./min)</th>
<th>Arterial oxygen saturation (%)</th>
<th>Arterial CO₂ (vol. %)</th>
<th>Hematocrit (%)</th>
<th>Plasma volume (ml./Kg)</th>
<th>A-V O₂ difference (vol. %)</th>
<th>Minute ventilation (L./min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>June</td>
<td>27</td>
<td>3</td>
<td>12</td>
<td>81</td>
<td>88</td>
<td>55</td>
<td>31</td>
<td>47</td>
<td>25</td>
<td>83</td>
</tr>
<tr>
<td>August</td>
<td>77</td>
<td>5</td>
<td>—</td>
<td>33</td>
<td>79</td>
<td>26</td>
<td>37</td>
<td>45</td>
<td>67</td>
<td>119</td>
</tr>
<tr>
<td>October</td>
<td>107</td>
<td>27</td>
<td>—</td>
<td>19</td>
<td>85</td>
<td>44</td>
<td>34</td>
<td>56</td>
<td>67</td>
<td>71</td>
</tr>
<tr>
<td>December</td>
<td>104</td>
<td>39</td>
<td>—</td>
<td>14</td>
<td>68</td>
<td>61</td>
<td>32</td>
<td>49</td>
<td>71</td>
<td>30</td>
</tr>
</tbody>
</table>

Animal 19

June: 27 mm Hg, 3 mm Hg, 12 mm Hg, 81 L/min, 88%, 55 vol. %, 31%, 47 mm Hg, 25%.

Clinical observations of animal 3 in October revealed mild subcutaneous edema in the intermandibular space, but the animal failed to develop other clinical signs of right heart failure and survived the duration of the experiment. At necropsy there was marked dilation and hypertrophy of the right ventricle accompanied by chronic passive congestion of the liver.

Animal 2 also developed severe pulmonary hypertension with a final mean pulmonary arterial pressure greater than 90 mm. Hg. There were no clinical signs of congestive right heart failure, but necropsy revealed grossly perceptible right ventricular hypertrophy.

The pulmonary arterial pressure in animal...
PULMONARY HYPERTENSION

TABLE 3
Plasma Volume, Hematocrit, Arterial Oxygen Saturation, Arterial Carbon Dioxide, and Minute Ventilation

<table>
<thead>
<tr>
<th>Month</th>
<th>Group</th>
<th>Plasma volume (ml/Kg.)</th>
<th>Hematocrit (%)</th>
<th>Arterial O₂ saturation (%)</th>
<th>Arterial CO₂ volume (%)</th>
<th>Minute ventilation (L/min. BTPS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>June</td>
<td>C</td>
<td>43 ± 4</td>
<td>35 ± 2</td>
<td>89 ± 3</td>
<td>49 ± 5</td>
<td>60 ± 21</td>
</tr>
<tr>
<td>August</td>
<td>C</td>
<td>46 ± 4</td>
<td>36 ± 4</td>
<td>83 ± 1</td>
<td>48 ± 11</td>
<td>100 ± 47</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>40 ± 4**</td>
<td>40 ± 3*</td>
<td>86 ± 4**</td>
<td>49 ± 8</td>
<td>75 ± 12</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>43 ± 3</td>
<td>39 ± 2</td>
<td>84 ± 6†</td>
<td>45 ± 13</td>
<td>98 ± 16§</td>
</tr>
<tr>
<td>October</td>
<td>C</td>
<td>37 ± 3</td>
<td>40 ± 3</td>
<td>94 ± 2</td>
<td>48 ± 11</td>
<td>78 ± 24</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>43 ± 3***</td>
<td>38 ± 3</td>
<td>87 ± 4**</td>
<td>49 ± 3</td>
<td>74 ± 17</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>54 ± 9††, § 34 ± 4</td>
<td>86 ± 2††</td>
<td>45 ± 7</td>
<td>77 ± 8</td>
<td></td>
</tr>
<tr>
<td>December</td>
<td>C</td>
<td>39 ± 5</td>
<td>41 ± 3</td>
<td>94 ± 3</td>
<td>50 ± 4</td>
<td>74 ± 19</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>40 ± 2</td>
<td>42 ± 5</td>
<td>87 ± 3**</td>
<td>46 ± 4</td>
<td>78 ± 17</td>
</tr>
<tr>
<td></td>
<td>S</td>
<td>40 ± 61, § 37 ± 4</td>
<td>81 ± 9††</td>
<td>50 ± 8</td>
<td>67 ± 25</td>
<td></td>
</tr>
</tbody>
</table>

Group C = Controls (10).
Group M = Moderate hypertension (6).
Group S = Severe hypertension (4).
* = Comparing C versus M.
† = Comparing C versus S.
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One superscript = P < 0.05.
Two superscripts = P < 0.01.
Three superscripts = P < 0.001.

17 followed an intermediate course rising rapidly at first but leveling off in October and then decreasing slightly in December. At necropsy, there was no evidence of congestive heart failure, but the right ventricle was visibly hypertrophied.

Pulmonary Arterial Wedge and Right Atrial Pressures
The "wedge" pressure was not elevated above the control value for subgroup M. Wedge pressures were difficult to obtain and were more variable in subgroup S. However, high pulmonary arterial pressures were recorded at times when the wedge pressures were normal. Right atrial mean pressures were significantly elevated only in subgroup S, particularly in steers 19 and 3 when heart failure was present.

CARDIAC OUTPUT
The cardiac output was similar in the high and low altitude animals except that animal 19 had a decreased output associated with heart failure (table 2). The arteriovenous oxygen difference also behaved similarly for the two groups: there was an increase with time which may relate to the decreasing environmental temperatures. Since cardiac output showed no increase, the elevations in pulmonary arterial pressure reflect parallel increases in calculated pulmonary vascular resistance.

VENTILATORY MEASUREMENTS
A statistically significant decrease in the arterial oxygen saturation to approximately 86 per cent was present in the high altitude animals at each period of observation (table 3). Significant differences were not found in the arterial saturations between subgroup S and subgroup M. The lower mean value for subgroup S in December reflects the low arterial oxygen saturation (68 per cent) of animal 19, then in congestive failure.

The arterial carbon dioxide content was not significantly decreased nor the minute ventilation increased in the animals at high altitude when compared to the low altitude controls.

HEMATOCRIT AND PLASMA VOLUME
During the six months of the experiment, there was an increase in hematocrit of similar magnitude for both the low and high altitude animals (tables 2 and 3). Consequently, polycythemia attributable to altitude could not be demonstrated. Considerable variations...
were observed in the plasma volume; however, the changes presented no constant pattern or trend, and there was no consistent difference between the high and low altitude groups.

**Body Weight**

Commencing with the October measurements, the high altitude group showed a significant and progressively lower rate of gain in body weight than did the control animals. The average weight gain of each animal during the six months at high altitude was 45 Kg., which was less than half the average individual gain of 102 Kg. for the low altitude control group.

**Right Ventricular Hypertrophy**

A significant increase in the weight ratio of the right ventricle to the total ventricular mass (RV/T ratio) was found in the high altitude group (0.32) when compared with the low altitude control lot (0.24). Hearts from the animals with severe pulmonary hypertension showed a significant elevation in the RV/T ratio (0.40) when compared with both the control lot and with the remaining animals in the high altitude group (0.28). Hearts from the animals in the altitude lot which exhibited moderate pulmonary hypertension showed significant elevation in the RV/T ratio when compared with those from the control lot. A close relationship existed between the RV/T ratio and the final pulmonary arterial pressure measurements, with a correlation coefficient of \( r = 0.95 \).

**Effects of Oxygen Administration**

Administration of 100 per cent oxygen by mask for 10 minutes to animal 12 in subgroup M resulted in a prompt fall in mean pulmonary arterial pressure from 46 to 34 mm. Hg. In animal 3 of subgroup S, oxygen reduced the pressure promptly from 131 to 94 mm. Hg, but no further. In both cases the pressures returned within five minutes to their initial values when the oxygen mask was removed.

**Discussion**

Pulmonary hypertension developed in each of 10 normal cattle taken to an altitude of 10,000 feet. The results have shown that several factors capable of elevating the pulmonary arterial pressure were probably not responsible for the pulmonary hypertension observed in this study. These factors are summarized as follows: (a) there was no significant increase in cardiac output; (b) severe pulmonary hypertension developed in the absence of a significantly elevated "wedge" pressure; (c) the blood viscosity was probably not increased since the hematocrit was similar for both the high and low altitude animals; (d) significant pulmonary hypertension preceded any observed increase in blood volume; (e) in the absence of heart failure, the right atrial and "wedge" pressures were normal, implying no increase in intrapleural pressure. Therefore, it is considered that the pulmonary hypertension was the result of an increased resistance to blood flow through the lungs. This probably reflected a reduction in the total cross-sectional area of the pulmonary vascular bed at the precapillary level.

The object of this experiment was to ascertain if normal cattle taken to high altitude develop pulmonary hypertension, and if so, to determine its possible etiology. The experimental design permitted the exclusion of the effects of diet, excessive salt intake, increased muscular activity, and genetic background. The data presented also eliminated environmental temperature as a primary causative factor.

The animals at high altitude could be differentiated from those at low altitude only by their arterial oxygen desaturation and their elevated pulmonary arterial pressures. The reduced partial pressure of atmospheric oxygen at 10,000 feet (\( pO_2 = 110 \) mm. Hg) as opposed to 5,000 feet (\( pO_2 = 130 \) mm. Hg) appeared to be the principal factor responsible for the pulmonary hypertension. In these animals at high altitude, the pulmonary vascular resistance remained elevated during the hypoxic stimulus and was lowered only when the hypoxia was reduced by administration of 100 per cent oxygen. In one animal with moderate hypertension, oxygen admin-
istration caused the pulmonary arterial pressure to be reduced to near normal. In an animal with severe pulmonary hypertension, oxygen administration also caused a large decrease in the pulmonary arterial pressure but considerable hypertension persisted. As observed in one nonexperimental animal with high mountain disease, only when the hypoxic stimulus was removed for several months by removing the animal to a lower altitude did complete regression of the pulmonary hypertension occur. An initial rapid decrease in pressure occurred followed by a slow progressive decline to normal values over a 10-month period. All of these observations point to the important role of hypoxia in the production of pulmonary hypertension in cattle. The hypertension developed in the presence of hypoxia and regressed when the hypoxia was removed.

It is not clear why some of the cattle at high altitude developed only moderate pulmonary hypertension, while others under identical conditions developed severe hypertension. No measurement other than the level of the pulmonary arterial pressure served to differentiate these two groups of animals. It is hoped that examination of the pulmonary vasculature by appropriate histopathological techniques will demonstrate whether consistent structural changes occurred.

**Summary**

Six months residence at an altitude of 10,000 feet produced significant pulmonary hypertension and arterial oxygen desaturation (86 per cent) in 10 normal steers born at 3,600 feet. Six of these animals, during the course of the experiment, showed a rise in mean pulmonary arterial pressure from 27 to 45 mm. Hg. The remaining four animals developed more severe pulmonary hypertension, and two with mean pressures greater than 100 mm. Hg had right heart failure. All 10 showed right ventricular hypertrophy proportional to the degree of pulmonary hypertension. Ten steers of similar age and origin, maintained as controls at 5,000 feet, showed a mean pulmonary arterial pressure of 27 mm. Hg throughout the experiment. The pulmonary hypertension observed at high altitude is considered to be due to an increased pulmonary vascular resistance resulting from a reduction in the total cross-sectional area of the pulmonary vascular bed. Chronic hypoxia appeared to be the most important etiological factor responsible for initiating the hypertension. The observed beneficial effects of 100 per cent oxygen inhalation and the prompt recovery of an affected animal when moved to lower altitude supported the concept of pulmonary hypertension induced by hypoxia.

**References**