Pulmonary Arteriosclerosis and Cor Pulmonale Due to Recurrent Thromboembolism

By P. J. Barnard, M.D., M.R.C.P.(E)

A long-term experiment will be described which has shown that repeated injections of minute autogenous blood clots in rabbits caused pulmonary arteriosclerosis and cor pulmonale. Pulmonary arterial lesions were of two main kinds with respect to circumference of the intimal coat: eccentric, ascribable to intimal incorporation of clot, and circumferential, probably ascribable to hypertension and vasospasm. A counterpart to this animal experiment is probably to be found in human pathology, as suggested by certain case reports, by the pathology of lymphangitis carcinomatosa and by evidence that circulating blood is not clot free.

Evidence has now accumulated that incorporation of blood clot into arterial intima might as well be a cause as a result of arteriosclerosis. Those who have studied large human systemic arteries from this thrombogenic viewpoint agree that all aspects of intimal arteriosclerosis including atheroma can follow incorporation of blood clot.1-4 Because red cell envelopes are rich in lipid, it is suggested that their breakdown supplies much of the fatty material in arteriosclerosis.1, 5 Experiments on the effects of blood clot emboli in pulmonary arteries, though showing that fibrous and elastic tissue form intimaly, have not produced atheroma.6-9 It is, however, possible that pulmonary arteries might differ from systemic arteries in their response to blood clot. (Pulmonary artery pressure is much lower than systemic pressure and pulmonary arteries transport venous blood.) Also, atheroma is exceedingly rare in veins. Furthermore, because atheroma both in pulmonary and systemic arteries is mostly limited to large elastic branches, this disease was perhaps not to be expected because the blood clot emboli used experimentally were far too small to lodge in vessels the size of elastic arteries.

The following experiments were undertaken to study afresh the effects of blood clot on the pulmonary arteries, and it is argued that thromboembolism could account for some human cases in which arteriosclerosis largely confined to pulmonary arteries is associated with cor pulmonale.

Material and Methods

Twenty young full-grown rabbits of various colors and both sexes, weighing 2.4 to 3.7 Kg. were used. Sixteen received fibrin emboli and four red clot emboli.

Preparation of Emboli

Fibrin emboli were prepared as follows: By incising marginal ear vessels with a safety razor blade, 1.6 ml. of blood was collected in a tube containing 0.2 ml. of 3.8 per cent sodium citrate solution. After spinning this blood at 2,500 revolutions per minute for five minutes, the plasma was pipetted into 10 ml. of calcium chloride, 0.025 molar solution. The clot that formed was dipped in physiologic saline, transferred to a petri dish and moulded with a glass rod flattened at one end to a disc lying in a pool of serum. The serum kept fibrin fragments together while they were chopped fine with a safety razor blade, a maneuver easily completed in 60 seconds.

After tilting the dish slightly, chopped up fragments were washed to the edge (by squirting 2 ml. of normal saline through a needle) whence they were aspirated directly through the syringe nozzle. (With practice, few fragments failed to reach the barrel.) Fibrin so prepared was then injected into an ear vein. This dose of fibrin, which is the amount contained in 1.6 ml. of blood, was administered twice weekly on Mondays and Thursdays, though on several occasions a week, and once, a month elapsed between injections. Each rabbit received fibrin from its own blood. To preserve veins, ears were used alternately for bleeding and injection, injections being carried out as distally as possible and preferably through the previous puncture mark. Ear incisions were also made through or close to previous incisions. Such precautions make it possible to bleed from and inject marginal veins almost indefinitely. After each rabbit had been given 10 injections, rabbits 5 and 13 were killed to find out if arterial lesions had been produced. From sections of their

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lungs it seemed likely that induction of extensive oblitative vascular disease would require many more injections. After 15 injections rabbit 11 developed fulminating conjunctivitis for which it had to be destroyed 13 days later. It received no more injections during this time. Another animal rabbit 8, which was found paralyzed in its hindquarters after the sixteenth injection, died nine days later, but postmortem examination failed to establish the cause. None of these four had developed cor pulmonale. Three days after each animal’s thirty fifth injection rabbit 7, breathless for some 14 days, died. The cause was established as pulmonary arteriosclerosis and chronic cor pulmonale. At this stage the remaining animals, all outwardly normal, were divided into two groups. The first group, consisting of six animals (rabbits 1, 2, 4, 6, 12 and 15), was set aside and received no more fibrin. These rabbits were killed 150 days later, and though all had developed pulmonary arteriosclerosis, none had cor pulmonale. The second group, consisting of 5 animals (rabbits 3, 9, 10, 14 and 16), was injected as before. At the sixty fifth injection respiratory distress was present in all for some 30 minutes or so following injection, though in rabbit 9 alone was discomfort severe. It died two days after the sixty fifth injection from chronic cor pulmonale. The remaining four (rabbits 3, 10, 14 and 16) were then given five more injections each. Rabbits 10 and 14 died 5 and 20 days, respectively, after the seventieth injection from cor pulmonale. Rabbits 3 and 16, after being allowed to run about in a large room for two months, were killed. The number and kind of injections each animal received, length of time during which fibrin fragments were injected and the time lapse between the final injection and death of each animal are summarized in table 1.

Red blood clot emboli were prepared from 0.75 ml. of autogenous blood allowed to clot spontaneously. After retraction the clot was chopped up and injected at the same time intervals as for rabbits receiving fibrin. As one rabbit of the four became slightly distressed following 15 injections, all subsequent doses of red clot fragments were prepared from 0.5 ml. of blood. This latter dose was chosen only because it caused no obvious distress. These rabbits received 60 injections each. Respiratory distress was only observed after the final few injections each rabbit received. They were then allowed to run about for two months before they were killed.

**Measurement of Fibrin Fragments**

Fibrin fragments prepared from each of 10 control rabbits were discharged on glass slides and the coverslips ringed with grease. Greatest diameters only of the first 100 fragments encountered on each slide were then measured using an eyepiece micrometer, and the 1,000 fragments classified into the size ranges: greater than 1.0 mm., 1.0 to 0.1 mm. and less than 0.1 mm. Their percentage size distribution is set out in table 2, as is the distribution in the same size ranges of the 3,488 arterial lesions found in sections prepared from the lungs of experimental animals. The purpose of this is discussed under Results.

**Arterial Circumferences and Ventricular Weights**

Twenty healthy rabbits of various colors, both sexes, and at least 1 year old, to correspond with the
Fibrin emboli (1000)......  3%  50%  38%  
Arterial lesions (3488)......  1%  68%  31%  

TABLE 3.—(20 Control Rabbits and 20 Experimental Rabbits) Arterial Circumferences and Ventricular Weights

<table>
<thead>
<tr>
<th>Rabbit No.</th>
<th>Arterial circumferences (mm.)</th>
<th>Right ventricle X 100 Left ventricle + Septum Gm. %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aorta</td>
<td>Pulmonary artery</td>
<td></td>
</tr>
<tr>
<td>Control rabbits (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>12</td>
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<tr>
<td>5</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>14</td>
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<tr>
<td>7</td>
<td>13</td>
<td>15</td>
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<tr>
<td>8</td>
<td>14</td>
<td>13</td>
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<tr>
<td>9</td>
<td>12</td>
<td>13</td>
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<tr>
<td>10</td>
<td>15</td>
<td>15</td>
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<tr>
<td>11</td>
<td>15</td>
<td>15</td>
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<tr>
<td>12</td>
<td>14</td>
<td>16</td>
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<tr>
<td>13</td>
<td>13</td>
<td>13</td>
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<tr>
<td>14</td>
<td>13</td>
<td>15</td>
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<tr>
<td>15</td>
<td>11</td>
<td>12</td>
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<tr>
<td>16</td>
<td>12</td>
<td>14</td>
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<tr>
<td>17</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>18</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>19</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>20</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Mean</td>
<td>12.5</td>
<td>13.4</td>
</tr>
<tr>
<td>SD</td>
<td>0.54</td>
<td>1.97</td>
</tr>
</tbody>
</table>

Experimental rabbits without cor pulmonale (10) fibrin

| 1          | 15                            | 13                                               | 20.03                                      |
| 2          | 15                            | 16                                               | 24.90                                      |
| 4          | 14                            | 16                                               | 24.02                                      |
| 5          | 11                            | 13                                               | 23.70                                      |
| 6          | 16                            | 18                                               | 25.05                                      |
| 8          | 11                            | 14                                               | 25.31                                      |
| 10         | 10                            | 14                                               | 24.20                                      |
| 12         | 12                            | 14                                               | 22.27                                      |
| 13         | 13                            | 13                                               | 24.60                                      |
| 15         | 14                            | 16                                               | 25.76                                      |
| Mean       | 13.2                          | 14.7                                             | 23.98                                      |
| S D.       | 2.0                           | 1.7                                              | 1.7                                        |

Experimental rabbits with cor pulmonale (6) fibrin, (4) red clot

| 3          | 15                            | 18                                               | 31.01                                      |
| 7          | 12                            | 23                                               | 50.07                                      |
| 9          | 14                            | 18                                               | 50.51                                      |
| 10         | 16                            | 20                                               | 34.79                                      |
| 14         | 14                            | 22                                               | 36.09                                      |
| 16         | 14                            | 17                                               | 29.62                                      |
| 17         | 14                            | 18                                               | 33.78                                      |
| 18         | 13                            | 16                                               | 31.85                                      |
| 19         | 15                            | 15                                               | 34.50                                      |
| 20         | 12                            | 14                                               | 35.85                                      |
| Mean       | 13.9                          | 18.1                                             | 36.61                                      |
| SD         | 1.3                           | 2.8                                              | 7.4                                        |

Standard Deviation = \( \sqrt{\frac{n}{n-1}} \)

Age of the experimental animals at the time of death, were kept under the same conditions as experimental rabbits. They were then killed and their hearts, lungs, kidneys and livers removed. After fixing for four days in 4 per cent neutral formaldehyde solution, the hearts were dissected by the method of Fulton and coworkers, ventricles being weighed separately. Because the right ventricle is relatively thin and joins the interventricular septum at about right angles, it could be dissected free with some accuracy; not so, however, the left ventricle, which is relatively much thicker and merges imperceptibly with the septum at an acute angle. For this reason right ventricular weight has been expressed as a percentage of septal and left ventricular weights combined. Narrow rings were cut from aorta and pulmonary artery immediately above their respective cusps, severed, and measured lying flat on a millimeter scale. Ventricular weights and arterial circumferences in control and in experimental animals are listed in table 3.

Measurement of Right and Left Ventricular Blood Pressures

This was done in 10 normal rabbits, five with and five without intravenous Nembutal anesthesia. Pressures were secured by direct ventricular puncture, using a Sanborn electromanometer and direct writing recorder. Since anesthesia was found to effect changes in right ventricular pressures only slightly, the experimental animals were studied without an anesthetic. An attempt was made to measure pressures in both ventricles, as the pressure difference was used to confirm that the right ventricle had actually been
TABLE 4.—Right Ventricular Blood Pressures (mm. Hg) in Control and Experimental Rabbits

<table>
<thead>
<tr>
<th>No.</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Mean</th>
<th>No.</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Mean</th>
<th>*CP</th>
<th>No. of doses</th>
<th>Time interval after final injections at which readings were taken (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33.0</td>
<td>0</td>
<td>19.0</td>
<td>1</td>
<td>29.0</td>
<td>0</td>
<td>12.0</td>
<td></td>
<td>35</td>
<td>160</td>
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<tr>
<td>2</td>
<td>37.0</td>
<td>0</td>
<td>10.0</td>
<td>2</td>
<td>31.0</td>
<td>0</td>
<td>14.4</td>
<td></td>
<td>35</td>
<td>160</td>
</tr>
<tr>
<td>3</td>
<td>22.0</td>
<td>0</td>
<td>9.2</td>
<td>3</td>
<td>24.0</td>
<td>0</td>
<td>12.0</td>
<td></td>
<td>70</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>31.5</td>
<td>-7</td>
<td>11.0</td>
<td>6</td>
<td>29.0</td>
<td>0</td>
<td>14.4</td>
<td></td>
<td>35</td>
<td>160</td>
</tr>
<tr>
<td>5</td>
<td>30.0</td>
<td>0</td>
<td>13.5</td>
<td>10</td>
<td>32.0</td>
<td>?</td>
<td>11.5</td>
<td></td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>27.0</td>
<td>0</td>
<td>12.0</td>
<td>12</td>
<td>26.0</td>
<td>0</td>
<td>7.2</td>
<td></td>
<td>35</td>
<td>160</td>
</tr>
<tr>
<td>7</td>
<td>24.0</td>
<td>0</td>
<td>11.0</td>
<td>14</td>
<td>84.0</td>
<td>-2.4</td>
<td>36.0</td>
<td></td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>21.0</td>
<td>-4</td>
<td>5.4</td>
<td>15</td>
<td>21.5</td>
<td>+2.4</td>
<td>11.0</td>
<td></td>
<td>35</td>
<td>160</td>
</tr>
<tr>
<td>9</td>
<td>21.5</td>
<td>-2.7</td>
<td>11.0</td>
<td>16</td>
<td>24.0</td>
<td>0</td>
<td>12.0</td>
<td></td>
<td>70</td>
<td>62</td>
</tr>
<tr>
<td>10</td>
<td>27.0</td>
<td>+2.7</td>
<td>13.5</td>
<td>17</td>
<td>21.0</td>
<td>+4.8</td>
<td>12.0</td>
<td></td>
<td>60</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>-1.1</td>
<td>11.5</td>
<td>19</td>
<td>39.0</td>
<td>0</td>
<td>17.0</td>
<td></td>
<td>60</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>5.02</td>
<td>7.07</td>
<td>20</td>
<td>95.0</td>
<td>0</td>
<td>35.0</td>
<td></td>
<td>60</td>
<td>62</td>
</tr>
</tbody>
</table>

Standard Deviation = \( \sigma = \sqrt{\frac{n}{n-1}} \).

* CP: Cor Pulmonale

entered. Only right ventricular pressures appear in table 4.

Measurements

**Medial thickness** of pulmonary arteries was measured both in control and experimental animals, using preparations stained with Weigert-van Gieson. The method is summarized diagrammatically:

(a) **Medial thickness**  (b) **External diameter**

(Mean of 1, 2, 3 and 4)  (Mean of 1 and 2)

Mean medial thickness (a) was expressed as a percentage of mean external diameter (b). Only arteries with circular or nearly circular outlines were measured. Because arteries exhibited varying amounts of contraction as judged by degree to which the internal elastic lamina was corrugated, true medial thickness was taken to be the distance between troughs of corrugations and outer edge of the medial coat. A total of 100 sections from different parts of the lungs of 14 control rabbits was used to measure the first 100 arteries encountered in cross section in each of the size ranges 1.0 to 0.1 mm. and less than 0.1 mm. external diameter. Arteries larger than 1.0 mm. were so few as to make measurement impracticable. By comparing these with similar measurements in fibrin-injected animals it was hoped to discover if medial hypertrophy had resulted from recurrent thromboembolism. Similar measurements were not made on red-clot injected rabbits because they were too few in number. Fibrin-injected animals were divided into those with and those without right ventricular hypertrophy. All pulmonary arterial lesions encountered in cross section in lung sections of these two groups were measured and classified into the same size ranges as for controls. This was done to find out if there was any difference in medial thickness of pulmonary arteries in animals that had developed cor pulmonale and also if any difference affected arteries of one size range only. The number of vessels in each size range measured in control and experimental rabbits as well as the results are recorded in table 5.

**Classification of Arterial Lesions**

The 1,859 pulmonary arterial lesions encountered in the lung sections of rabbits with cor pulmonale were classified into size ranges: greater than 1.0 mm., 1.0 to 0.1 mm. and less than 0.1 mm., and into the types of lesion listed in table 6. In rabbits without cor pulmonale 1,629 arterial lesions were similarly classified.

**Fibrinolytic Activity in Peripheral Blood**

This was tested for by the method of MacFarlane and Pilling. Blood samples were withdrawn by cardiac puncture in five groups each consisting of two control rabbits, at time intervals of 1/2, 1, 2, 6 and 24 hours, respectively, after injection of fibrin
fragments prepared from 1.6 ml. of blood. In a further five groups, each consisting of two control rabbits, autogenous red clot fragments prepared from 0.5 ml. of blood were injected and blood samples withdrawn for examination at the same time intervals as before. These experiments showed that emboli of either kind did not produce detectable fibrinolytic activity in peripheral blood.

**Table 5.—(Rabbits 1–16) Medial Thickness of Pulmonary Arteries in Control and Experimental Rabbits Expressed as a Percentage of External Diameter**

<table>
<thead>
<tr>
<th>Arteries</th>
<th>Control rabbits (14)</th>
<th>Rabbis without cor pulmonale (10)</th>
<th>Rabbis with cor pulmonale (6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteries &lt;0.1 mm...</td>
<td>100 6.2 1.5</td>
<td>101 6.9 4.1 0.434</td>
<td>84 7.6 5.2 0.847</td>
</tr>
<tr>
<td>Arteries 0.1-1.0 mm...</td>
<td>100 12.5 6.3</td>
<td>103 12.4 6.2 0.877</td>
<td>73 4.2 0.7 0.171</td>
</tr>
</tbody>
</table>

The standard error of difference between means is:

\[ \sqrt{\frac{s^2_c + s^2_e}{n_c n_e}} \]

where \( s^2_c \) stands for control animals, \( s^2_e \) for experimental animals.

**Preparation and Staining of Sections**

Lungs, kidneys and livers both of control and of experimental rabbits were fixed in 4 per cent neutral formaldehyde solution. Lower lobes of lungs were each divided into three portions, but other lobes were embedded whole. All sections were stained with Weigert–van Gieson and sometimes hematoxylin-eosin as well. Frozen sections from the lungs of rabbits that had received fibrin injections were stained for fat with Sudan III and compared with similar sections from rabbits that had received red clot injections.

**Results**

**Rabbits 1–16: Fibrin Emboli**

**Rabbits Without Cor Pulmonale:** (Rabbits 1, 2, 4, 5, 6, 8, 11, 12, 13 and 15.) All rabbits that had received 35 injections or less (except rabbit 7) showed no abnormality at postmortem examination apart from the lungs; though outwardly normal, their cut surfaces were studded with thickened arteries. Circumferences both of aorta and pulmonary artery were within normal limits. Right ventricular pressures of rabbits in which tracings were secured were within the normal range four months after final injection of emboli and one month prior to killing (table 4). Microscopic examination revealed extensive arteriosclerosis, but as pulmonary arterial lesions were similar in structure to those in animals with cor pulmonale, no separate description of them will be given here.

**Table 6.—(Rabbits 1–16) Incidence of Arterial Lesions**

<table>
<thead>
<tr>
<th>Types of lesion</th>
<th>&gt;1.0 mm.</th>
<th>1.0 to 0.1 mm.</th>
<th>&lt;0.1 mm.</th>
<th>Totals</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With CP</td>
<td>Without CP</td>
<td>With CP</td>
<td>Without CP</td>
<td>With CP</td>
</tr>
<tr>
<td>Circumferential intimal fibrosis</td>
<td>7 4</td>
<td>277 265</td>
<td>170 139</td>
<td>454 408</td>
<td>24.4</td>
</tr>
<tr>
<td>Eccentric intimal fibrosis</td>
<td>8 2</td>
<td>168 183</td>
<td>69 89</td>
<td>245 274</td>
<td>13.2</td>
</tr>
<tr>
<td>Circumferential fibro-elastic thickening</td>
<td>5 2</td>
<td>289 236</td>
<td>99 152</td>
<td>393 390</td>
<td>21.1</td>
</tr>
<tr>
<td>Eccentric fibro-elastic thickening</td>
<td>6 16</td>
<td>185 184</td>
<td>30 167</td>
<td>221 367</td>
<td>11.9</td>
</tr>
<tr>
<td>Medial scarring</td>
<td>0 0</td>
<td>182 75</td>
<td>61 9</td>
<td>243 84</td>
<td>13.1</td>
</tr>
<tr>
<td>Recanalization</td>
<td>1 4</td>
<td>252 87</td>
<td>50 15</td>
<td>303 106</td>
<td>16.3</td>
</tr>
<tr>
<td>Totals</td>
<td>27 28</td>
<td>1353 1030</td>
<td>479 571</td>
<td>1829 1629</td>
<td>100.0</td>
</tr>
<tr>
<td>Grand totals and percentages</td>
<td>55 or 1%</td>
<td>2383 or 68%</td>
<td>1050 or 31%</td>
<td>3488 or 100%</td>
<td>1859 or 100%</td>
</tr>
</tbody>
</table>

* CP: Cor Pulmonale.
Rabbits with cor pulmonale: (Rabbits 3, 7, 9, 10, 14 and 16.) All rabbits that had received 70 injections each (rabbits 3, 10, 14 and 16), one rabbit that had received 65 (rabbit 9) and one that had received 35 (rabbit 7) showed cor pulmonale at postmortem examination. Of these, rabbits 7, 9, 10 and 14 died from cor pulmonale, but rabbits 3 and 16 were killed 62 days after their final injection. Cor pulmonale, which was diagnosed by the naked eye in these six as well as in the four rabbits (rabbits 17, 18, 19 and 20) that received red clot emboli, is also reflected in the figures for right ventricular weights, all of which were above normal (last column of table 3). However, only rabbits 7 and 9 had pronounced right ventricular hypertrophy. Though the mean pulmonary arterial circumference reflects dilatation in animals with cor pulmonale as a group, dilatation was obvious to the naked eye only in rabbits 7 and 14, both of which died from cor pulmonale. The high mean value is attributable mainly to the measurements from these two animals.

Right ventricular pressures were secured in the rabbits listed in table 4. Only rabbits 14 and 20 (readings taken two days after the seventieth injection of fibrin emboli and 62 days after the sixtieth injection of red clot emboli respectively) had marked elevation of right ventricular systolic and mean pressure.

In rabbits that eventually died from cor pulmonale (rabbits 7, 9, 10 and 14), but especially the first two (both of them albinos) skin and mucous membranes were found to be so blue that they could have been called “black cardia.” Polycythemia was evident because the supernatant layer of plasma after spinning down citrated blood for preparation of emboli was far narrower than it had been at the beginning of the experiment.

Animals dying from cor pulmonale (except rabbit 10) in contrast to rabbits 13 and 16, in which right ventricular hypertrophy without signs of failure was found on killing, also showed ascites, bilateral hydrothorax, in one animal (rabbit 7) hydropericardium, and passive venous congestion of the abdominal viscera. In all animals pleural lung surfaces were normal, but cut surfaces showed widespread thickening of arteries (fig. 1). Apart from passive venous congestion, organs other than heart and lungs appeared normal. Right ventricular hypertrophy is illustrated in figure 2.

**Fig. 1. Rabbit 14. Lower lobe of left lung showing prominence of divided arteries. (Approximately life size.)**

**Fig. 2. Rabbit 7. Hypertrophy of right ventricle and dilatation of pulmonary artery. (× 4 approximately.)**

**Microscopic appearances of lungs.** (Rabbits 1–16.) Arteries. Classification of the 3,488 arterial lesions showed that they were most numerous in arteries 1.0 to 0.1 mm. in external diameter (68 per cent), next numerous in arteries less than 0.1 mm. (31 per cent) and least numerous in arteries greater than 1.0 mm. (1
per cent). Size distribution of fibrin emboli also shows that they were likely to have lodged in about the same proportions in arteries of these size ranges (table 2). This correspondence does not necessarily mean that lesions were brought about by intimal incorporation of fibrin. Thus lesions due to vasospasm would also be most numerous in arteries of that size range in which most emboli became impacted.

Arterial lesions (1,850 in animals with and 1,629 in animals without cor pulmonale) were classified as follows: (a) Circumferential intimal fibrosis (endarteritis obliterans or endarteritis fibrosa) (figs. 4, 6, 7, 9 and 10). Compare with the contracted though otherwise normal vessels in figures 3 and 5. (b) Eccentric intimal fibrosis (figs. 11 and 12). (c) Circumferential fibroelastic intimal thickening which included elastosis (figs. 14, 15 and 16). (d) Eccentric fibroelastic intimal thickening (fig. 17). (e) Medial scarring (fig. 13). (f) Recanalization (fig. 18).

“Circumferential” meant that a lesion was present all around the intimal periphery. Lesions of this type had inner contours that were either smooth (figs. 7, 8, 9, 14, 15 and 16) or scalloped (figs. 4, 6 and 10). “Eccentric,” on the other hand, meant that intimal thickening was present at one or more places on the intimal circumference, the rest of the intima being normal (figs. 12 and 17). The term “fibrosis” signified that elastic tissue either was wholly absent or present only in small amount (figs. 6, 7 and 10), and the term “fibroelastic” that new elastic tissue and fibrous tissue were present in about equal amounts (fig. 14). For purposes of classification this term also included less frequent lesions depicted as “elastosis” (figs. 8, 15 and 16), which were composed of elastic laminae set concentrically and in which van Gieson’s stain revealed little collagen. “Medial scarring” (fig. 13) referred to segmental replacement of muscle by collagen, and “recanalization,” partition of vascular lumens by septa consisting either of fibrous or fibroelastic tissue (fig. 18). Very occasionally a compartment showed formation of a new intraluminal artery complete with muscular media and internal elastic lamina. Reference to table 6 shows that the relative proportions of lesions classified as circumferential intimal fibrosis, eccentric intimal fibrosis and circumferential fibroelastic thickening in arteries of the three sizes taken together were about the same whether or not cor pulmonale was present. Medial scarring and recanalizations were, however, proportionally at least twice as numerous, and eccentric fibroelastic intimal thickening only half as numerous in animals with cor pulmonale as in the rest. Though these results seem to be significant, I cannot explain them because factors such as vasospasm, hypertension and possibly hypoxemia, which it will be argued caused most vascular damage, are so complexly interrelated.

Analysis of table 5 shows that there was no medial hypertrophy of pulmonary arteries in the 10 rabbits without cor pulmonale and that atrophy was actually present in rabbits with cor pulmonale. Because arterial media was often very thin, especially in arteries of less than 0.1 mm., medial thickness in these rabbits was even less than figures show. Even though some of this medial “thinning” was due to arterial dilatation, figures are not vitiated, because this contingency was allowed for by the method adopted in taking measurements. Medial thinning was doubtless also favored by the weakening effect of the transmedial vascularization observed in larger arteries at sites opposite intimal thickenings. Though a thin medial coat was sometimes associated with scarring, it most often just “faded” away, a process accompanied by loss of staining affinity (figs. 15, 17 and 18). Slight increase of adventitial collagen was present in some arteries with medial scarring. There was no kind of arterial lesion distinctive among animals with cor pulmonale.

Fat staining showed no sudanophilic material in any arterial lesion. Fibrin emboli undergoing organization were found in the lungs of all animals that died or were killed 20 days or less after the last injection. Some of these lesions were infiltrated by more neutrophils than uncomplicated organization alone could be expected to cause. No eosinophil infiltration was present, and no abscess formation. The lesion was not considered to be a foreign body reaction as in a previous thromboembolic
Fig. 3. Control Rabbit 1. Normal contracted artery showing folding of intima and radial arrangement of endothelial cells. (Hematoxylin-eosin × 220.)

Fig. 4. Rabbit 12. Circumferential scalloped intimal fibrosis with radial orientation of collagen at right. (Weigert-van Gieson × 144.)

Fig. 5. Control rabbit 8. Normal contracted artery showing folding of internal elastic lamina. (Weigert-van Gieson × 220.)

Fig. 6. Rabbit 6. Dense circumferential intimal fibrosis (endarteritis obliterans). (Weigert-van Gieson × 275.)

Fig. 7. Rabbit 4. Circumferential intimal thickening with smooth inner contour consisting predominantly of fibrous tissue. (Weigert-van Gieson × 181.)

Fig. 8. Rabbit 2. Minute muscular artery showing elastosis. (Weigert-van Gieson × 275.)
experiment in which fibrin was prepared for injection by grinding. Accidental bacterial contamination might explain these arterial lesions, because fibrin, once prepared, could not be sterilized for fear of altering its properties. Since aseptic precautions were observed, risk of contamination, even during bleeding, cannot have been great. Sensitization to fibrin was improbable, as similar lesions had been found in rabbits receiving autogenous fibrin in a single dose only. No explanation of the rather heavy neutrophilic infiltration of some organizing lesions is, therefore, apparent.

Precapillary vessels, which are endothelial tubes wholly or partially surrounded by an elastic lamina, developed lesions which, though of the same kind in all rabbits, were more numerous in rabbits with cor pulmonale. Endothelial swelling was the mildest change, but was not accompanied by proliferation of the cells. More severe damage was present as eccentric or circumferential formation of a substance reacting pale pink to van Gieson’s stain. Such lesions were sometimes accompanied by formation of an additional elastic lamina.

Capillaries were normal except for dilatation in rabbits dying with cor pulmonale.

Veins were normal except in rabbits with cor pulmonale, abnormality taking the form of dilatation and intimal formation of a substance like that in precapillary vessels. No arteriovenous anastomoses were observed in the lungs of any animal.

Bronchial tree and alveolar walls were normal except in animals dying of cor pulmonale, in which alveolar edema was encountered. Interstitial fibrosis was not observed.

Rabbits 17–20: Red Clot Emboli

All showed pulmonary arteriosclerosis indistinguishable from that in rabbits receiving fibrin. Though all four rabbits had cor pulmonale, only rabbit 20 had pulmonary hypertension as well. The finding of cor pulmonale without hypertension in three of them suggests that right ventricular hypertrophy once established from thromboembolism of the lungs, persists, even though pulmonary pressures may return to normal.

Although it was anticipated that lesions induced by red clots would have greater fat content than fibrin-induced lesions, because red cell envelopes are rich in lipoid, this was not so. No rabbit developed atheroma. This, however, does not prove that atherosclerosis cannot be caused by blood clot in systemic arteries.

Arteries of organs other than lungs appeared normal.

The lungs of one control rabbit showed sparsely distributed eccentric intimal fibrosis.

Evidence that Only a Portion of the Blood Clot Injected Was Retained in the Lungs. From the amount of fibrin per dose and the number of injections given, it was calculated that fibrin emboli and red clot emboli from the following total amounts of blood, respectively, were necessary to cause cor pulmonale:

56 ml.......rabbit 7.
104 ml.......rabbit 9.
112 ml.......rabbits 3, 10, 14 and 16.
34 ml.......rabbits 17, 18, 19 and 20.

Thus it was found that cor pulmonale was produced by red clot from a total volume of blood smaller than the volume of plasma needed to produce fibrin clot that would have the same effect. This might be due to the fact that, volume for volume, a greater bulk of clot is to be obtained from whole blood than from plasma. Because of red cell content alone, the amount of red clot obtainable from 34 ml of whole blood must have been at least half this volume. Such an amount of red clot is large in relation to the capacity of a rabbit’s pulmonary arterial tree. It is, therefore, probable that only a portion of the clot given to rabbits 17, 18, 19 and 20 was actually incorporated in pulmonary arterial intima or they would not have survived as long as they did. That the lungs of rabbits do not retain all the red clot injected into them has also been observed by Heard. Except that an intravascular clot in man may “disappear” and that patency of vascular lumens is re-established after blood clot occlusion by re-canalization or by incorporation into arterial intima, nothing definite is known about the fate of thromboemboli. Despite my failure to demonstrate freely circulating fibrinolysin (plasmin) after injection of emboli, it is pos-
sible that fibrinolysis was actually taking place within the lungs and that any fibrinolysis passing into the general circulation was inactivated. Wright and co-workers,\textsuperscript{15} who attempted to demonstrate circulating fibrinolysis after producing clots in the ear veins of rabbits, also had no success.

**DISCUSSION**

If rabbits are given a single dose of fibrin emboli and killed 24 days later, eccentric fibrous tissue intimal thickenings containing new elastic fibers are the only lesions which result in the pulmonary arteries.\textsuperscript{9} This kind of lesion has accordingly been ascribed to organization of fibrin into arterial intima; other kinds of lesion in these experimental rabbits must, therefore, have been due to something else. Even supposing that circumferential lesions had resulted from central recanalization of occluding emboli, this explanation would not hold good for development of those nicely concentric elastic laminae illustrated in figures 8, 14, 15 and 16. Hypertension, vasospasm and hypoxemia are other probable mechanisms in the development of such lesions.

A disease such as mitral stenosis which secondarily induces pulmonary hypertension is commonly associated with arteriosclerosis involving intima right around the lumen.\textsuperscript{14, 15} Because of this it is thought that hypertension contributed to arteriosclerosis even though only two rabbits had obviously elevated pulmonary blood pressure at time of measurement. In the others, transitory hypertension could have been present following each injection of emboli. Even though hypertension as such cannot be separated from vasospasm in causing circumferential arterial lesions, it is accepted that vasospasm causes hypertension in systemic arteries. Furthermore, numerous studies on early cases of secondary pulmonary hypertension have shown that this form of hypertension also has a reversible element which can be attributed to vasospasm.\textsuperscript{16-19} That such vasospasm need not be of central nervous origin is evident from studies on heart-lung preparations.\textsuperscript{20, 21} Moreover, pulmonary vasospasm appears to be causatively related to anoxemia. Pulmonary hypertension can be rapidly induced in normal subjects by causing them to breathe 10 per cent oxygen for short periods, the hypertension returning equally rapidly to normal when the low oxygen breathing is stopped. This is attributable to vasospasm.\textsuperscript{22} In four cats exposed in a decompression chamber for about two weeks to low oxygen tension in the inspired air, the muscular coats of pulmonary arteries were found hypertrophied.\textsuperscript{23} Conversely, it has been shown by von Euler and Liljestrand\textsuperscript{24} that in cats the breathing of pure oxygen caused a marked drop in pulmonary arterial pressure. Though it is not known how hypertension and vasospasm bring about arteriosclerosis, it is conceivable that the circumferential lesions which they cause depend upon disturbed arterial nutrition. Rotter\textsuperscript{25} and others whom he quotes, believe that arteriosclerosis is produced by defective supply of nutritive lymph to those parts like intima which have no capillaries. This opinion is based upon observation of endarteritis obliterans in the edematous zone of anemic infarcts. It is also maintained that

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**Fig. 9.** Rabbit 7. Loose circumferential intimal fibrosis with smooth inner contour. (Weigert-van Gieson \(\times 181\).)

**Fig. 10.** Rabbit 4. Scalloped circumferential intimal fibrosis with development of new elastic laminae faintly discernible. (Weigert-van Gieson \(\times 181\).)

**Fig. 11.** Rabbit 4. Eccentric, mainly fibrous intimal thickenings. That to the left is partially divided by an elastic membrane suggesting successive incorporations of fibrin. (Weigert-van Gieson \(\times 144\).)

**Fig. 12.** Rabbit 1. Eccentric intimal fibrosis with development of new elastic tissue faintly discernable. Note segmental destruction of internal elastic lamina and media at 5 o'clock. (Weigert-van Gieson \(\times 181\).)

**Fig. 13.** Rabbit 11. A combined circumferential intimal lesion: fibrosis at 6 o'clock with fibroelastic thickening involving rest of circumference. Medial scarring is also present on the left. (Weigert-van Gieson \(\times 144\).)

**Fig. 14.** Rabbit 4. Circumferential intimal thickening composed of fibrous and elastic tissue disposed in alternate layers. (Weigert-van Gieson \(\times 181\).)
Figs. 9–14
Fig. 15. Rabbit 8. Intimal thickening composed almost wholly of concentric elastic laminae. Animal killed to terminate experiment. No cor pulmonale. (Weigert-van Gieson X 144.)

Fig. 16. Rabbit 7. Elastosis (compare fig. 15). This animal died of cor pulmonale. (Weigert-van Gieson X 144.)

Fig. 17. Rabbit 7. Eccentric fibroelastic intimal thickening: media shows loss of staining affinity. (Weigert-van Gieson X 144.)

Fig. 18. Rabbit 7. Recanalization with fibroelastic septa: note medial loss of staining affinity. (Weigert-van Gieson X 144.)
hypertension, by overstretching arterial walls, embarrasses diffusion of nutritive lymph, so accounting for the well-known association of severe arteriosclerosis with persistent elevation of blood pressure in systemic arteries. de Langen26 also argues that mechanical interference with nutrition of arterial walls is the primary factor causing arteriosclerosis. It is possible that spasm of small muscular arteries, in contrast to stretching of large elastic arteries, would have the same effect in impairing intimal nutrition. Figures 3 and 5 show contracted pulmonary arteries from normal rabbits with resultant intimal folding and radial instead of parallel arrangement of endothelial cells in respect to arterial circumference. Comparison of these figures with that from an experimental rabbit (fig. 4) showing nodular circumferential intimal fibrosis strongly suggests that spasm had caused this particular lesion. Moreover, radial arrangement of collagen in this figure provides evidence not only that endothelial cells form collagen, but that their orientation determines direction in which this substance is laid down. In similar manner, orientation of fibroblasts in regenerating tendon appears to control the pattern of collagen fibers.27

Though hypertension and vasospasm are held to be chiefly responsible for the development of arteriosclerosis in recurrent thromboembolism, it is possible that polycythemia and hypoxemia added their embarrassing circulatory effects, which are hypertension, hypervolemia, and high blood viscosity.28, 19 Thus rabbit 10 died with right ventricular hypertrophy and dilatation but without transudate in serous cavities, an observation not uncommon in cases of primary pulmonary arteriosclerosis and hypertension. In some case reports of primary pulmonary arteriosclerosis and hypertension, intimal thickening has been regarded as compensatory to congenital medial hypoplasia.29-32 This interpretation of arteriosclerosis does not, however, fit the present experiment, which has shown that intimal thickening precedes medial atrophy, not the other way about.

I have interpreted the course of events culminating in chronic right ventricular failure as follows: Recurrent embolism by minute blood clot emboli causes eccentric intimal fibrosis. At the same time recurrent vasospasm due to impaction of emboli in arteries then brings about hypertension and impaired intimal nutrition, so that circumferential and concentric lesions consisting not only of fibrous but of elastic tissue also arise. Lesions arising during recurrent embolic vasospastic hypertension remain once they have formed, as in animals, killed five months after the thirty-fifth injection, in which hypertension was absent. Should, however, arteriosclerosis become sufficiently severe or should hypoxemia set in, vasospasm and hypertension, previously recurrent, become continuous. This leads in turn to rapid advance of arteriosclerosis, and thus is a vicious circle established with progressive right ventricular hypertrophy and eventual failure. This complex interrelationship between thromboembolism and cor pulmonale is here set out diagrammatically: heavy arrows indicate that vasospasm was predominant in initiating arteriosclerosis and cor pulmonale; light arrows indicate the effects that thrombogenic arteriosclerosis and hypoxemia might have exerted as well.

If fibrin or red clot embolism occurring over a protracted period is capable of inducing severe pulmonary arteriosclerosis and cor pulmonale in animals which presumably have a normal mechanism of ridding their vessels of clot, the danger must be far greater in those animals or in man in whom this mechanism is defective. This is one reason for thinking that some human cases of primary pulmonary arteriosclerosis need not be a disorder of blood vessels to start with.

Primary pulmonary arteriosclerosis might be a disorder of blood caused by repeated and protracted pulmonary embolism of showers of minute clots from systemic veins where condi-
tions are favorable for intravascular coagulation. If such emboli formed in systemic venous blood, few would pass the pulmonary arterial filter, and thus significant arteriosclerosis would be confined to the lungs. Embolic experiments aimed at discovering the role blood clot plays in causing pulmonary arteriosclerosis would have added significance if lesions could also be brought about by injecting substances which would cause clotting in circulating blood. If rabbits are given repeated intravenous injections of thromboplastin extract either alone or mixed with Russell viper venom, fibrin emboli become arrested in pulmonary arteries and undergo organization resulting in connective tissue intimal thickening sometimes containing new elastic fibers. Other lesions, probably anaphylactic, are encountered at the same time because the coagulants used contained foreign protein. These experiments have the value of demonstrating that sublethal doses of coagulants will cause lesions which, though scanty, are like those found in human cases of pulmonary arteriosclerosis. Schneider has furthermore shown that both placental trauma to rabbits and human abruptio placentae can cause acute cor pulmonale from fibrin embolism. Intravascular deposition of fibrin after premature separation of the normally implanted placenta has also been observed by McKay and coworkers.

In 1939, Belt wrote: "It seems to me that stenosing lesions of the pulmonary arteries may sometimes be caused by minute embolisms occurring perhaps over long intervals." Cases of recurrent thromboembolism with right ventricular hypertrophy have only been recognized when emboli were large, mainly because of their size and because at autopsy their source is easier to demonstrate than that of small emboli would be. But among case reports of recurrent thromboembolism examples may be chosen which illustrate occlusion of pulmonary arteries from the largest to the smallest. Case reports which for example have described embolic occlusion of the main stem or its large branches are those of Belt, Carroll and Petch. Embolism of medium-sized arteries has been described by Castleman and Bland and in a Cabot case report, and embolism of small arteries by Eppinger and Wagner and by Goedel, whose cases showed arteriosclerosis and clots at arterial branching points. Mantz and Craig have described a case of right ventricular hypertrophy ascribable to organization of small thromboemboli widely scattered in small pulmonary arteries where emboli had their source in what was probably a congenital portocav shunt. Furthermore, it is not unlikely that some cases recorded as primary pulmonary hypertension might have been due to chronic thromboembolism because organizing blood clots were regarded as secondary to the arteriosclerosis. If thrombi are always ascribed to arteriosclerosis, not the other way about, then thromboembolic arteriosclerosis is bound to escape notice.

Chronic cor pulmonale may also be associated with widespread organizing thrombosis of small intrapulmonary arteries due to carcinomatous emboli. In 1947, Saphir wrote, "It is clear that diffuse thickening of the intima, the result of organized mural thrombi, closely resembles and often cannot be distinguished from pulmonary arteriosclerosis." From a case such as that of Schmidt (cited by Brill and Robertson), in which cor pulmonale was due to widespread thrombosis of small pulmonary arteries, cancer cells being encountered nowhere else in the lung except in arteries, it is probable that lymphatic or parenchymal involvement is not necessary for development of arterial lesions. A case of mucoid lymphangitis carcinomatosa without cor pulmonale studied personally showed widespread eccentric intimal fibrosis of small pulmonary arteries (figs. 19, 21, 22 and 23). Intimal thickenings sometimes contained new elastic fibers, but even when elastic tissue was present the collagenous component nearly always predominated. Intimal lesions were associated with varying degrees of distortion and destruction of the intimal elastic laminae (figs. 19 and 23). Some arteries were completely occluded by fibroelastic tissue. The media was usually intact, but in places this layer was scarred and merged with adventitia, which coat sometimes exhibited increase of collagen.
FIG. 19. Human pulmonary artery: Circumferential mainly fibrous intimal thickening. (Weigert-van Gieson × 80.)

FIG. 20. Human pulmonary artery showing fibroelastic obliteration. (Weigert-van Gieson × 80.)

FIG. 21. Human pulmonary artery showing eccentric fibrous intimal thickening: note compression into star-shaped form by surrounding mucoid lymphatic infiltration. (Weigert-van Gieson × 80.)
Fig. 22. Human pulmonary artery showing eccentric fibrous intimal thickening. (Weigert-van Gieson × 181.)

Fig. 23. Human pulmonary artery: eccentric fibrous intimal thickening containing irregularly disposed elastic fibers. (Weigert-van Gieson × 220.)

Fig. 24. Human pulmonary arteries containing organizing blood clot. (Weigert-van Gieson × 80.)

Fig. 25. Small human pulmonary artery partially occluded by fibrin containing carcinoma cells. (Weigert-van Gieson × 220.)
On the basis of the experiment recorded in this paper, these lesions were ascribed to organization mainly of fibrin clot which was seen in all stages in numerous small arteries (figs. 24 and 25). Clots were found both with and without associated carcinomatous emboli.

Even in normal people circulating blood is perhaps not as clot-free as is supposed. The comparatively rapid turnover of platelets, prothrombin and fibrinogen suggests this. Other indirect evidence that blood might be coagulating continuously comes from Sternberger,19 who claims to have recovered active thrombin from circulating blood by dissociating it from antithrombin. Elevation of recoverable thrombin would be expected to indicate clinical conditions in which fibrin formation is increased. An increase of circulating thrombin is also observed postoperatively and in various thrombotic states and may also be associated with other disorders. Furthermore, the wide variety of conditions in which circulating fibrinolysin can be demonstrated also supports the belief that intravascular coagulation is far commoner than general opinion now holds.50, 51 The observation of an elevated antifibrinolytic titer in blood after exposure to cold possibly may be correlated with development of intravascular thrombosis observed in frostbite. It is believed a high antifibrinolysin titer represents a response to the presence of excessive fibrinolysin which in turn might indicate thrombosis.52, 53 Guest and associates54 have reported increased antifibrinolytic activity in certain clinical states in some of which the possibility of thrombosis existed. Another disease in which numerous blood clots or arteriosclerosis may be found in small arteries is sickle cell anemia. Yater and Hansmann55 described two cases with hypertrophy and failure of the right heart.

It seems likely that once pathologists become generally aware of how varied thromboembolic arterial lesions really can be, cases otherwise attributable only to primary hypertension will diminish. Study of case reports, however, shows that there are cases which at the present time cannot be ascribed to anything but essential hypertension in the sense that this term applies also to systemic hypertension. However, hypertension in both lesser and greater circulations can remain essential only so long as its causes remain obscure. Further study must thus eventually lead to progressive recognition of symptomatic hypertension in both circuits.

Summary and Conclusions

A long-term experiment has shown that repeated intravenous injections of minute autogenous blood clots into rabbits caused pulmonary arteriosclerosis and cor pulmonale. Intimal incorporation of clot accounted only for eccentric intimal fibrosis sometimes containing new elastic fibers. This is a small fraction of the total lesions caused thromboembolically. All other lesions were circumferential and composed of fibrous tissue by itself (endarteritis obliterans) or of fibrous tissue with new elastic laminae in addition (fibroelastosis); they were ascribed to hypertension and vasospasm. Whether rabbits received repeated injections of fibrin particles or red clot particles, pulmonary arterial lesions were the same. Atherosclerosis was not encountered. Also, medial atrophy was caused by recurrent thromboembolism, not medial hypertrophy. No arterial lesion was specific for animals that developed cor pulmonale.

That this animal experiment has its counterpart in human pathology is supported by case reports, a case of pulmonary lymphangitis carcinomatosa, and evidence that circulating blood is not clot free.

Sumario Español

Un experimento por largo término ha demostrado que repetidas inyecciones de pequeños coágulos autógenos de sangre a conejos causó arteriosclerosis pulmonar y cor pulmonale. La incorporación del coágulo a la íntima explicó solamente fibrosis excentérica de la íntima algunas veces conteniendo nuevas fibras elásticas. Estas fueron solamente una pequeña fracción de las lesiones totales causadas tromboembólicamente. Todas las otras lesiones fueron circunferenciales y compuestas de tejido fibroso ensí (endarteritis obliterans) o de tejido fibroso con
nuevas láminas elásticas en adición (fibroelastosis); fueron atribuidas a hipertensión y vasoespasmo. Las lesiones arteriales pulmonares fueron iguales no obstante las repetidas inyecciones de partículas de fibrina o partículas de coágulo de sangre. No se encontró ateroesclerosis. También se causó atrofia de la media y no hipertrofia con el tromboembolismo recurrente. No hubo una lesión específica en los animales que desarrollaron cor pulmonale.

Este experimento animal tiene su duplicado en la patología humana es ostenso por casos informados, un caso de linfangitis pulmonar carcinomatosa y evidencia de que la sangre en circulación no está libre de coágulos.

ACKNOWLEDGMENTS

I am indebted to Professor J. Barnetson for his assistance and to Dr. Andries Brink for determinations of ventricular pressures. For all technical work including photography, I thank my wife, a stipendiary of the South African Council for Scientific and Industrial Research, an organization to which I furthermore owe especial gratitude for defraying all other costs in connection with this work.

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Pulmonary Arteriosclerosis and Cor Pulmonale Due to Recurrent Thromboembolism
P. J. BARNARD

Circulation. 1954;10:343-361
doi: 10.1161/01.CIR.10.3.343
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
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