The Effects of Increased Intracranial Pressure on the Pulmonary Circulation in Relation to Pulmonary Edema

By William Harrison, M.D., and Averill A. Liebow, M.D.

Sudden elevation of intracranial pressure raises not only the systemic but also the pulmonary intravascular pressures, on occasion, sufficiently to result in pulmonary edema. At least two mechanisms are concerned, that of bradycardia, and that of left ventricular failure. Evidence is presented that interruption of vagal inflow temporarily abolishes the first mechanism. These observations are considered in relation to the clinical problem of head injury.

A CLASSIC experimental study of the effects of increased intracranial pressure upon the systemic arterial tension was published by Harvey Cushing\(^1\)\(^-\)\(^2\) some 50 years ago. More recently the observation that pulmonary edema often accompanies traumatic or spontaneous cerebral hemorrhage\(^3\) has prompted an investigation of the consequences of increased intracranial tension for the lesser circulation. While the present work was in progress, the publications of Campbell and Visscher and their colleagues\(^4\)\(^-\)\(^6\) appeared; the results of their studies will be compared with observations made in the course of the present work. The results of simpler experiments which have concerned themselves merely with the effect of a sudden rise of intracranial pressure in the production of pulmonary edema have been contradictory, those of Surtshin, Katz, and Rodbard\(^7\) denying an association in the dog, while MacKay\(^8\) claimed to have produced pulmonary edema within 30 seconds after applying a crushing trauma to the skull in the rat. Some of the contradictions may have to do with the divergent criteria that have been employed for judging the existence of pulmonary edema.

Methods

In the present experiments dogs weighing 7 to 20 Kg. were employed under alpha-chloralose anesthesia (50 mg. per kilogram), supplemented before

From the Department of Pathology, Yale University School of Medicine, New Haven, Conn., in contract with the Office of Naval Research, as Project N6ori-44, Task Order XI.
paction of the midbrain against the tentorium was considered to be an undesirable and unpredictable complication. Sudden death sometimes resulted after a very slight increment of pressure within the bag, presumably from herniation of the brain. That local pressure upon the brain is not necessarily transmitted equally to all parts of the cranial cavity was noted by Cushing in his early work. Fluid compression was finally used, therefore, by one of the two methods. This produced a more uniform compression but had the disadvantage of introducing additional fluid into the dog, sometimes in large quantity. The intracisternal introduction of the fluid with the needle, or even with the catheter, is fraught with the danger of damage to the brain during the introduction, or by some subsequent accident with displacement either into the cerebral substance, or out of the cisternal space. The most generally satisfactory was Cushing's original method, whereby a 1 cm. button is trephined from the left vertex, the dura opened, and a tightly fitting threaded metal tube is screwed into the skull. Tyrode's solution is then forced through the tube to compress the cerebrum from a large pressure bottle regulated by a side-escape mercury valve. Pressure in the bottle is maintained at a level remarkably constant and regulable by keeping compressed air constantly bubbling through the escape valve. The pressure to which the solution is subjected is read on a mercury manometer, and recorded by means of one of the Hamilton manometers together with the four vascular pressures. At the end of each experiment of the cerebral compression type a needle is inserted into the cisterna magna to confirm free communication of pressure from vertex to the perimedullary space. Tyrode's solution at pH 7.4 was employed for the cerebral compression rather than saline, since in our experience saline at pH 7, when introduced into the subdural or subarachnoid space produced a progressive hyperpnea.

The experiments were performed with a tracheotomy tube in place, for it has been suggested that laryngospasm might lead to phases of inspiratory obstruction with a more negative intra-alveolar pressure that would favor the development of pulmonary edema, or phases of expiratory obstruction with a high intrathoracic pressure, and the tube furthermore effectively excluded the aspiration of saliva or other secretions from the pharynx.

Oxygen was administered during the course of some of the experiments, especially when there was marked bradycardia or bradypnea. Its use will be discussed.

Necropsies were performed within minutes after the death of the animal. The increase in weight of the lungs that may occur post mortem when they are allowed to remain in the thorax has been described by Durlacher. The heart was promptly opened to confirm the position of the needles that had been left within their guides, and blood was aspirated into a suction bottle before it had clotted. It was seen that a tunnel of connective tissue had formed about the needle guides, with obliteration of the fissures between the left upper and lower lobes, and that there were tenuous fibrous adhesions in the region of the wound, but without generalized obliteration of the left pleural space or pericardial sac. The lungs were weighed together with a segment of trachea 5 cm. in length, and after dissecting away the left auricle, trunk of the pulmonary artery, and enlarged bronchial lymph nodes. The lung weight was expressed as a percentage of the body weight, the normal range except in the hot summer being 0.80 to 1.20. The existence of congestion and edema was graded according to the following scale: Questionable: 1.20-1.40, Slight: 1.41-1.60, Moderate: 1.61-2.00, Severe: Above 2.01. Microscopic sections were made when the lung weights exceeded 1.20 per cent. Even in some of the heavier lungs, the presence of edema was indicated not by any large quantity of acidophilic coagulum within the alveoli, but by an increase in the width of the septa and in the perivascular and peribronchial collars of areolar tissue. Similar observations were made in this laboratory and elsewhere of the pulmonary edema that follows the administration of alpha-naphthyl thioura (ANTU) in the dog. Only rarely was bubbling fluid obvious in the bronchi and trachea of the dogs in the present experiment. Rales also may not be heard, despite obvious edema post mortem. Although the lung weight–body weight ratio is not an entirely satisfactory method of detecting pulmonary edema, it is by far the most objective. Gross examination is too easily susceptible to prejudice. When edema is present, there is loss of the pale salmon-pink color of the normal lung which is replaced by dull red-grey, less spongy and resilient, doughy noncrepitant tissue. These changes were first apparent chiefly in the dependent portions of the lungs near the hilum, especially on the medial aspects. Obviously, a contribution to any increase in the weight of the lungs may be made by a greater content of blood. In the technic of preparation, almost all of the blood is removed from the larger vessels which are thus left in the collapsed state. In retrospect, perhaps the best method to separate the contribution made by the two would be to measure the increase in iron content in relation to the increase in total weight of the lung above normal. Since it is clear from the experiments of Cushing that increased intracranial pressure stimulates both the parasympathetic and sympathetic mechanisms, the effects of atropinization and cervical vagotomy in altering the response to the cerebral compression were examined. In addition, the effects of bilateral cervical vagotomy alone were observed without cerebral compression as in Farber's experiments in this last group the amount of parenteral fluid was purposely varied. Two dogs received abundant saline, approximately 100 cc. per kilogram per hour,
while in three others saline was administered in smaller amounts.

**Observations**

**Effects of Raising Intracranial Pressure**

The sequence of events when the intracranial pressure is rapidly raised may be illustrated in an experiment (serial No. 4, table 1) in which a subdural bag was rapidly expanded (fig. 1). In this experiment attempts had been made unsuccessfully for some hours to increase the intracranial pressure by expanding a polyethylene bag which had been placed epidurally at a previous operation. This bag was then removed and another polyethylene bag was inserted beneath the dura which was sewn over it. Control records were obtained (fig. 1, sect. 1). Water under pressure controlled manometrically was then introduced into the bag. A detailed protocol of the experiment follows:

6:07 p.m. (fig. 1, sect. 1) With the bag uninflated the femoral artery pressure varied between 192/95 and 192/78 mm. Hg; the mean left atrial pressure was 115 cm. H2O, and the pulmonary artery pressure 46/10 to 51/16 cm. H2O.

6:20 p.m. (fig. 1, sect. 2) Bag pressure to 120 mm. Hg. Femoral artery pressure rose at once to 200/100-128, but without significant change in left atrial and pulmonary artery pressure.

6:40 p.m. (fig. 1, sect. 3) Bag pressure to 160 mm. Hg. Within 10 seconds bradycardia appeared, during which the heart rate fell to 36, but there were alternating phases during which the heart rate accelerated to 72 for three or four beats. During the slow beats the systemic diastolic pressure was very low (30) and the pulse pressure was very large (systolic 174); as the heart accelerated the diastolic pressure rose to approximately 100 while the systolic remained the same. During these cycles the respirations were also slow. As Campbell and co-workers have described, at the onset of bradycardia the left atrial pressure rose at once, in this instance to a mean of 21 with an accompanying rise in the pulmonary artery pressure.

### Table 1.—Factors in Development of Pulmonary Edema

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Body Weight</th>
<th>Length of Experiment</th>
<th>Parenteral Fluid</th>
<th>L.W. × 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.9</td>
<td>3.5</td>
<td>16</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>13.2</td>
<td>4.7</td>
<td>23*</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>10.4</td>
<td>3.0</td>
<td>76*</td>
<td>1.20</td>
</tr>
<tr>
<td>4</td>
<td>12.2</td>
<td>7.0</td>
<td>24*</td>
<td>1.46</td>
</tr>
</tbody>
</table>

### Cisternal Fluid Compression

<table>
<thead>
<tr>
<th>Body No.</th>
<th>Body Weight</th>
<th>Length of Experiment</th>
<th>Parenteral Fluid</th>
<th>L.W. × 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>10.0</td>
<td>3.0</td>
<td>76*</td>
<td>.91</td>
</tr>
<tr>
<td>6</td>
<td>16.8</td>
<td>3.5</td>
<td>26</td>
<td>.94</td>
</tr>
<tr>
<td>7</td>
<td>19.9</td>
<td>7.5</td>
<td>30*</td>
<td>.97</td>
</tr>
<tr>
<td>8</td>
<td>17.7</td>
<td>5.0</td>
<td>34*</td>
<td>1.00</td>
</tr>
<tr>
<td>9</td>
<td>10.9</td>
<td>2.5</td>
<td>57*</td>
<td>1.04</td>
</tr>
<tr>
<td>10</td>
<td>10.7</td>
<td>5.7</td>
<td>28*</td>
<td>1.30</td>
</tr>
<tr>
<td>11</td>
<td>15.9</td>
<td>7.0</td>
<td>19*</td>
<td>2.71</td>
</tr>
</tbody>
</table>

### Supratentorial Fluid Compression + Atropine

<table>
<thead>
<tr>
<th>Body No.</th>
<th>Body Weight</th>
<th>Length of Experiment</th>
<th>Parenteral Fluid</th>
<th>L.W. × 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>13.5</td>
<td>2.0</td>
<td>58*</td>
<td>.99</td>
</tr>
<tr>
<td>22</td>
<td>17.9</td>
<td>3.0</td>
<td>37</td>
<td>1.04</td>
</tr>
<tr>
<td>23</td>
<td>9.1</td>
<td>5.0</td>
<td>59</td>
<td>1.08</td>
</tr>
<tr>
<td>24</td>
<td>12.2</td>
<td>5.5</td>
<td>55</td>
<td>1.12</td>
</tr>
<tr>
<td>25</td>
<td>10.0</td>
<td>2.0</td>
<td>65</td>
<td>1.19</td>
</tr>
<tr>
<td>26</td>
<td>8.6</td>
<td>1.0</td>
<td>79*</td>
<td>1.23</td>
</tr>
<tr>
<td>27</td>
<td>9.3</td>
<td>2.5</td>
<td>71*</td>
<td>1.73</td>
</tr>
<tr>
<td>28</td>
<td>15.9</td>
<td>3.5</td>
<td>107</td>
<td>2.20</td>
</tr>
</tbody>
</table>

### Table 1.—(Continued)

<table>
<thead>
<tr>
<th>Supratentorial Fluid Compression + Vagotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial Fluid Compression + Vagotomy</td>
</tr>
<tr>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Supratentorial Fluid Compression + Vagotomy</td>
</tr>
</tbody>
</table>

* Indicates estimate based on average saline inflow into cannulas of 5 cc./min., and, where applicable, on rate of inflow in drops per min. of Tyrode's solution used for cerebral compression (1 drop of Tyrode considered = 0.05 cc.).
7:00 p.m. (fig. 1, sect. 4) With a further increase in the pressure within the bag to 200 mm. Hg, the systemic arterial pressure ranged in the neighborhood of 200/38 and there was bradycardia associated with a continued rise in the mean left atrial pressure to 32.

7:12 p.m. (fig. 1, sect. 5) Bursts of tachycardia with systemic pressure falling, followed by apnea. Pressures in lesser circulation remained elevated.

7:14 p.m. (fig. 1, sect. 6) Sudden tachycardia, systemic pressure rose to 240/132 and left atrial pressure to a mean of 51. Mean pulmonary artery pressure was 60.

7:20 p.m. Dog going into shock. Dead at 7:26 p.m.

This animal was exceptional, in exhibiting no obvious pulmonary edema, although the mean left atrial pressure was maintained above 20 cm. H2O for approximately 30 minutes, with levels momentarily reaching 51.

In the present experiment there are demonstrated two phases in the elevation of the left atrial pressure. One is immediately consequent upon the induction of bradycardia. The other occurs late, in association with an extreme rise in systemic arterial pressure, and is presumably the result of incipient failure of the left heart. In some instances there is a slight rise in the mean left atrial pressure even before the bradycardia appears, particularly when there is a large elevation of the aortic pressure.

The sequence of pressure changes was similar by whatever means the intracranial pressure was increased. With fluid compression there was less delay than with the subdural bag, the pressure on the medulla could be accurately controlled, and sudden fatal herniation of the brain was avoided. Bradycardia, and sometimes apnea, was observed in these experi-

**EFFECTS OF INCREASED INTRACRANIAL PRESSURE ON CIRCULATION**

Fig. 1. Effects of increased intracranial pressure on circulation.
introduced intravenously.\textsuperscript{18, 19} Under these circumstances, also, the left atrial pressure can be made to rise to high levels, but this is accompanied by a rise in the systemic venous pressure; it is remarkable that here the pressure in the left atrium rose much higher than in the femoral vein, as in the observation made by Yeomans, Porter and Swank,\textsuperscript{18} and in our own observations.\textsuperscript{19} This is probably the result of the relative indistensibility of the left atriovenous system.\textsuperscript{20}

In summary of these observations, it may be said that edema of the lung, as measured by the objective criterion of lung weight in proportion to body weight was only occasionally produced by any of the three methods when neither atropine nor vagotomy had been instituted (table 2). In three of 20 experiments there was questionable edema, in one edema was slight, and in only one other, where the experiment had been carried on for seven hours, was the edema severe.

\textbf{Effects of Atropinization and Vagotomy}

Since the induction of bradycardia consequent to the elevation of the intracranial pressure appeared to be one of the mechanisms associated with an immediate rise in the left atrial pressure, it was considered of interest to observe the effects of interrupting the vagal pathways either with atropine or by low cervical vagotomy. Observations made during a typical atropinization experiment (serial No. 27, table 1) will now be detailed.

10:23 a.m. Dog 165. Weight 9.3 Kg. Systemic arterial blood sample taken: Oxygen saturation 99.2 per cent. Animal then anesthetized with 20 cc. chloralose, 25 mg. per cc., intravenously.

10:30 a.m. 3 cc. of 2 per cent sodium Pentothal given intravenously. Cannulation of arterial and venous systems of greater and lesser circulation performed. Tracheal tube placed.

11:27 a.m. Systemic arterial blood sample: Oxygen saturation 94.4 per cent. Head trephined and connected to pressure system.

12:33 p.m. Control record: Femoral artery pressure 168/134 mm. Hg; mean left atrial pressure 1 mm. Hg; mean pulmonary artery pressure 11 mm Hg; mean femoral vein pressure 3 mm. Hg. Dog hereafter on continuous oxygen at atmospheric pressure, via intratracheal tubes.

12:34 p.m. Intracranial pressure raised to 100 mm. Hg.

12:44 p.m. Intracranial pressure raised to 110 mm. Hg. Femoral artery pressure now 211/148 without significant changes in the other pressures.

12:49 p.m. Intracranial pressure raised to 120 mm. Hg. Four minutes after the rise, systemic pressure was 220/148; other pressures approximately the same as before.

12:54 p.m. Intracranial pressure raised to 133 mm. Hg. The animal now showed a leakage of fluid from the nose and the eyes were protuberant. Almost immediately after this last rise in intracranial pressure there was an irregular slowing of the heart as in fig. 1, sect. 3, with swings in the femoral diastolic pressure and an increase in the left atrial pressure. Bradycardia then became established.

1:01 p.m. The animal suddenly became apneic. During the next two minutes the heart rate was 48, the femoral artery pressure approximately 200/97, and the left atrial pressure became elevated to approximately 10 mm. Hg, while the mean pulmonary artery pressure was 12 and the femoral vein pressure had a mean of 6.

1:03 p.m. Atropine 0.6 mg. administered intravenously. The sequence of events is shown in a record reproduced in figure 2. Thirty seconds after the administration of the drug theortic diastolic and systolic pressures began to rise, accompanied by a transient rise in the pressures in the lesser circulation. Tachycardia (approximately 160) then occurred. Between 30 and 35 seconds after the atropine the first spontaneous respiration occurred indicated by the dip in the curves for the left atrial and pulmonary arterial pressures, following which the pressures in the lesser circulation

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Method of Increasing Intracranial Pressure & Total Number & \multicolumn{4}{c|}{L.W./B.W. \times 100} \\
\hline
Subdural Bag & 4 & 3 & 1 & 1 & \textbullet
\hline
Cisternal Fluid & 7 & 5 & 1 & 1 & \textbullet
\hline
Supratentorial Fluid & 9 & 7 & 2 & \textbullet & \textbullet
\hline
Supratentorial Fluid + Atropine & 8 & 5 & 1 & 1 & \textbullet & \textbullet
\hline
Supratentorial Fluid + Vagotomy & 3 & 1 & 1 & 2 & \textbullet
\hline
Vagotomy & 5 & 3 & \textbullet & \textbullet & \\
\hline
\end{tabular}
\caption{Lung Weight as Percentage of Body Weight in Dogs with Elevated Intracranial Pressures}
\end{table}
decreased while the femoral artery pressure was maintained at the very high level of 260/160. The femoral artery pressure elevated before the administration of atropine fell as soon as the atropine effect became manifest, and while the pressures in lesser circulation were still high.

1:12 p.m. Femoral artery pressure 222/144; left atrial pressure 1; femoral vein pressure 3.

1:13 p.m. Intracranial pressure raised to 135.

1:17 p.m. Femoral artery pressure 234/152-240/170.

Atropine, 0.6 mg., administered intravenously.

1:30 p.m. Intracranial pressure raised to 145.

1:40 p.m. Intracranial pressure raised to 155.

1:42 p.m. Pronounced Traube-Hering waves.

1:50 p.m. Respirations irregular with periods of apnea lasting as long as one minute.

2:04 p.m. Pronounced Traube-Hering waves with peaks at 271/193 and troughs at 193/120. Respirations irregular. Atropine, 0.6 mg., administered intravenously.

2:25 p.m. Intracranial pressure elevated to 165. The sequence of events following this last rise is indicated in the record reproduced in figure 3. The portions of records taken at 2:28 p.m., 2:39 p.m., 2:45 p.m., and 2:55 p.m. (30 minutes after the last rise in intracranial pressure) are shown. The first two records are divided into two parts, at the troughs and peaks of the Traube-Hering waves. It will be noted that pulsatile variations in the intracranial pressure were more prominent at the peaks of the Traube-Hering waves. At the peaks of these waves of systemic hypertension, the pressures in the lesser circulation tended to be high, but were not always in phase. There was, nevertheless, a general upward trend in the latter reaching and maintaining high levels between 14 and 20 minutes after the last rise in intracranial pressure until a terminal phase 10 minutes later.

2:30 p.m. Systemic arterial blood sample: Oxygen saturation 109.5 per cent in reference to hemoglobin.

2:55 p.m. Animal suddenly went into shock with a fall in the systemic arterial pressure and died a few minutes later. It is interesting to note during this last phase that all pressures were sagging, except that in the femoral vein which was rising and exhibiting a pronounced pulse. In this animal the lung weight–body weight ratio \( \times 100 = 1.73 \).

At the end of the experiment a needle was introduced into the cisterna magna and it was demonstrated by simultaneous records that the intracisternal pressure followed closely the level of the intracranial pressure as measured in the manometer connected to the Tyrode bottle and supratentorial trephine opening. This indicated free communication of pressure above the tentorium with the perimedullary cistern. In this experiment there was a moderate degree of pulmonary edema with a lung weight–body weight percentage of 1.73.

In each of seven experiments in which either atropine or vagotomy was employed the effects were similar. With the appearance of severe bradycardia and apnea the procedure rapidly restored respiration and there was a sudden tachycardia with high systolic and diastolic pressures, while the pressures in the lesser circulation quickly fell. It then became possible to raise the intracranial pressure to much higher levels (30 or more mm. Hg higher than before). Ultimately, however, there was evidence of failure of the left ventricle with a rise in the left atrial pressure.

Relation of Lung Weight–Body Weight Ratio to Pressure in the Left Auricle

It might be expected from observations of capillaries elsewhere that as the capillary pressure approached the onchotic pressure, exudation of fluid would be favored.

All nine dogs in the fluid compression experiments (table 1, serial Nos. 5–31) in whom
the lung weight exceeded 1.20 per cent of the body weight, induced elevations of the mean left atrial pressure in excess of 20 cm. H$_2$O had existed for at least 15 minutes, with capillary pressure slightly in excess of this level. In the 18 dogs with normal lung weight–body weight ratios, four had mean left atrial pressures above 20 cm. H$_2$O at some time. In the bag compression experiments all four animals before death showed at least transitory elevation of the left atrial pressure above 20 cm. H$_2$O. Usually this was terminal and was associated with the cerebral herniation that has been described. In one animal (serial No. 1, table 1), there was no pulmonary edema despite a left atrial pressure exceeding this level which had been maintained for approximately 25 minutes. Likewise in the report of Campbell and his colleagues$^5$ not all animals with high left atrial pressure exhibited pulmonary edema.

**Role of Infused Fluids**

Control experiments to be reported in detail elsewhere$^{29}$ in which Tyrode solution and saline were injected for a five hour period demonstrated that no more than questionable edema was produced when the injection rate was less than 80 cc. per kilogram per hour, and that even at rates as great as 100 cc. there might be no increase in lung weight above 1.20 per cent of body weight, although usually in the five hour period moderate or severe pulmonary edema was produced. At the rates of infusions prevailing in the cerebral compression, one might expect from observations of this control series a drop in the hematocrit of 10 to 20 per cent toward the end of a five hour period of observation. As shown by Yeomans, Porter and Swank,$^{22}$ there would be a comparable fall in the serum protein with a drop in onchotic pressure of 2.5 to 5 mm. Hg.

**Role of Vagotomv**

There has been controversy concerning the role of vagotomy in itself as a possible mechanism in the production of pulmonary edema. Farber$^{16}$ in experiments upon guinea pigs reported development of pulmonary edema after vagotomy alone, but in a subsequent report$^{17}$ detailing similar experiments in rabbits it was found that large quantities of fluid were necessary in addition to the vagotomy. In the present series it appeared that edema developed in dogs five to five and one-half hours after vagotomy only if a saline inflow approaching 100 cc. per kilogram per minute were administered (table 1, serial Nos. 32 to 36).

**Relation of Pulmonary Edema to the Administration of Oxygen.** Oxygen was used in some of the experiments and did not prevent the development of pulmonary edema, as shown in table 3, which summarizes the data from serial Nos. 1–31 (table 1). It is obvious in fact that oxygen was used more frequently in those animals which ultimately developed pulmonary edema, in order to counteract the effects of the ultimate drop in pressure and its effects of the extreme bradycardia and bradypnea characteristic of the course in these animals. Thus, the oxygen helped to keep these animals alive for an interval sufficiently long to permit the development of pulmonary edema associated with the pressure changes in the lesser circulation.

**Observations on Oxygen Saturation of the Systemic Arterial Blood.** It is stated that in the peripheral capillary bed anoxia is a factor favoring extravasation of fluid. Although relatively little is known of the influence of anoxia on the capillaries of the lung, this factor should nevertheless be considered in evaluating mechanisms of pulmonary edema.

In contrast with the severe anoxia that follows deep Pentobarbital anesthesia, the methods used in the present series of experiments proved superior. Under chloralose alone, in 12 observations, the oxygen saturation was found to vary between 93 and 100 per cent. With the sodium Pentothal supplement, the oxygen saturation in observations on six dogs was found to be as low as 89.6 per cent in one experiment, but above 90 per cent in all
others. As a rule the oxygen saturation fell less than 5 volumes per cent after the sodium Pentothal supplement, while the animal was breathing air. With oxygen breathing, the oxygen saturation before the development of pulmonary edema was usually in excess of 100 per cent in relation to hemoglobin, rising as high as 110.6 per cent in one instance.

Six determinations of oxygen saturation made within one half hour before death of the animals are summarized in table 4. In three animals, those with the highest lung weight-body weight ratios, there was some reduction in oxygen saturation. It is evident that anoxia was severe in but one animal, serial No. 36. It was, however, greater than the recorded value

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>O2 Administered†</th>
<th>Time of O2 Sample before Death</th>
<th>O2 Sat.</th>
<th>L.W./B.W. X 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>+</td>
<td>11</td>
<td>101.4</td>
<td>.50</td>
</tr>
<tr>
<td>34</td>
<td>-</td>
<td>30</td>
<td>100.0</td>
<td>1.12</td>
</tr>
<tr>
<td>27</td>
<td>+</td>
<td>25</td>
<td>109.5</td>
<td>1.73</td>
</tr>
<tr>
<td>31</td>
<td>+</td>
<td>5</td>
<td>88.0</td>
<td>1.91</td>
</tr>
<tr>
<td>35</td>
<td>-</td>
<td>20</td>
<td>90.0</td>
<td>2.20</td>
</tr>
<tr>
<td>36</td>
<td>-</td>
<td>5</td>
<td>&gt;34.3</td>
<td>2.30</td>
</tr>
</tbody>
</table>

* Serial numbers, as in table 1.
† + = Animal on O2; — = Animal breathing room air.

of 34.3 per cent saturation since this animal had received an enormous volume of fluid, 132 cc. per kilogram of body weight per hour for a five hour period, which would reduce the carbon monoxide capacity by about one half. In the calculation, the carbon monoxide capacity of the original preinfusion blood sample only was used, since the postinfusion capacity was not available.

**Discussion**

These observations lead to conclusions different from those of Campbell and his associates, in that pulmonary edema was only occasionally produced in the dog upon raising the intracranial pressure. The conditions of the experiment differed in that they employed sodium pentobarbital anesthesia, in the use of a balloon for increasing the intracranial pressure, and in other details. In the Minnesota report, moreover, the weights of the lungs in relation to the body weight were not given and the less objective criteria of gross and microscopic observation were the standards of measurement of the pulmonary edema. Nevertheless, in both series of observations it was possible to demonstrate an elevation of pulmonary capillary pressure, thereby establishing conditions favorable to the development of pulmonary edema. In the present experiments it was demonstrated that the left auricular pressure would become elevated not only in immediate association with bradycardia, but also after the heart had been caused to labor against the extreme hypertension produced by raising the intracranial pressure to high levels so slowly that bradycardia was avoided.

The immediate life-saving effect of atropine in interrupting parasympathetic inflow was apparent in the present observations, as in those of Campbell and his associates. In addition it was found that the animals would now tolerate an additional increment of 30 mm. Hg or more above that which had previously produced apnea and bradycardia, but that ultimately there was cardiac failure with a renewed increase in left atrial pressure with associated pulmonary edema. Thus, if the effect in patients is the same as in these experimental animals, atropine may provide a period of grace during which operative intervention may relieve the rising intracranial pressure.

As the gap between the capillary blood pressure in the lungs and the protein oncotic pressure becomes narrowed, it is obvious that additional factors tending to narrow this gap should be avoided. Among these factors are excessive infusion of fluids, especially of hypertonic crystalloids, or protein-containing solutions, and any reduction in intra-alveolar pressure such as might be associated with obstruction of the respiratory tract. In fact, tracheotomy has been suggested in the management of severe head injuries where unconsciousness is likely to persist for more than 24 hours.
EFFECTS OF INCREASED INTRACRANIAL PRESSURE

SUMMARY AND CONCLUSIONS

Study of the systemic and pulmonary intravascular pressures in dogs suggests the existence of a cardiopulmonary factor in the mechanism of death. A striking rise in the pressure within the left atrium may occur by two mechanisms (1) in immediate association with bradycardia as the intracranial pressure is elevated to levels ranging between 100 and 150 mm. Hg; (2) later, in association with an immense systemic hypertension resulting in accomodation to the rising intracranial pressure, even when this is so slow that bradycardia and apnea are avoided. Atropine, by interrupting bradycardia and apnea, permits an additional increment of intracranial pressure of 30 mm. Hg or more, but ultimately the left atrial pressure becomes elevated. Thus, the atropine provides a period of grace for adopting measures designed to lower intracranial pressure. As judged by the objective criteria of the ratio of lung weight to body weight, pulmonary edema is only occasionally produced, but especially in those animals where the left atrial pressure is maintained above 20 cm. H2O for more than 15 minutes. Nevertheless, as the margin between pulmonary intracapillary and onchotic pressure is reduced in consequence of the altered hemodynamics associated with cerebral compression, quantitative factors involving parenteral fluid, and intra-alveolar pressure become increasingly important.

REFERENCES

17. —: Neuropathic pulmonary edema. Arch. Path. 30: 180, 1940.
20. Harrison, W., and Liebow, A. A.: Effects of massive intravenous infusions with special reference to the lesser circulation. (To be published.)
The Effects of Increased Intracranial Pressure on the Pulmonary Circulation in Relation to Pulmonary Edema
WILLIAM HARRISON and AVERILL A. LIEBOW

Circulation. 1952;5:824-832
doi: 10.1161/01.CIR.5.6.824

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1952 American Heart Association, Inc. All rights reserved.
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:
http://circ.ahajournals.org/content/5/6/824

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/