It would appear that most, if not all, of the centrally induced pulmonary edemas are associated with strong stimulation of the central sympathetic mechanisms. The widespread distribution of pressor areas would account for the variety of procedures that produce edema. The pioneer work of Hess (1954) and the extensive studies of Magoun, Ranson and associates (1938, 1940) have explored the hypothalamus and have found the most sensitive areas for producing blood pressure changes to be in the medial forebrain bundle, the lateral hypothalamus, the perifornical nucleus and the H field of Ford. More recently, Gutman et al. (1962) stimulated discrete areas of the brain stem of unanesthetized rabbits from the hypothalamus to the medulla and found both pressor and depressor areas distributed throughout the whole brain stem. Experiments to date indicate that the most active area for edema production is the discrete "edemagenic" center described by Marie and Patton (1959). The simultaneous stimulation of several pressor sites as by the intracisternal injection of veratrine or a thrombin fibrinogen mixture may however summate to give a pressure response as rapidly developing and as great in magnitude as those from the "edemagenic" center.

REFERENCES


Pathogenesis of Postoperative Acute Pulmonary Edema of the Central Nervous Origin

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Postoperative pulmonary edema usually experienced by surgeons was not only
caused by the misuse of blood transfusion during or after operation of the cardiopulmonary diseases, but also caused by various operations of other diseases. Particularly, many cases occurred after an operation of the nervous diseases. Though postoperative pulmonary edema appeared in a very wide variety of conditions, it was classified into 3 groups according to the similarity of the histological findings: (1) that occurring after a brain operation as well as brain trauma, (2) that occurring after an operation of cases with cardiopulmonary diseases accompanied by pulmonary circulatory disturbances, and (3) that occurring after an abdominal operation of various diseases accompanied by metabolic disorder such as hypoproteinemia, anemia and hepatic or renal disturbance.

As to the features of the pulmonary edema occurring after an operation for diseases of the central nervous system, there appeared a marked congestion of the pulmonary vascular system and floating of red cells was found in the alveoli. The exudation of a liquid component in the alveoli was clearly seen. In the cases of pulmonary edema after an operation for cardiopulmonary diseases, a congestion of the pulmonary vascular system and hemorrhage into the alveoli were remarkable. This was particularly true in the cases where there was pulmonary hypertension before the operation. In such cases fibrosis of the blood vessels was seen in addition to the above mentioned hemorrhage and the congestion. Though the exudation of liquid component into the alveoli was also seen, its degree was much less than that in cases of brain lesions. In the cases of pulmonary edema after an operation of abdominal diseases accompanying hypoalbuminemia, anemia and hepatic or renal disturbance, the congestion was not remarkable, but a high degree of exudation of liquid component into the alveoli was observed.

In order to determine the incidence of these three types, a calculation was made about the ratios of the numbers of major brain, cardiopulmonary and abdominal operations to the numbers of occurrence of pulmonary edema. These were 12%, 3% and 1%, respectively. It is worthy of note that incidence of the postoperative pulmonary edema in brain surgery is significantly higher than those in other types of operations.

For the purpose of clarifying the relationship between the nervous system and the development of the pulmonary edema, an investigation about the innervation of the pulmonary vessels was performed. It was concluded that there were both higher and lower centers on the reflex arc which consists of afferent and efferent pathways of the pulmonary vascular innervation. The higher center of the reflex arc where the afferent pathway ascends the vagal nerve was situated in the nuclei of the preoptic areas. The efferent pathway starting from this center passed through the pons, the medulla and the upper spinal cord and, entering the efferent sympathetic nerve, was distributed to the pulmonary vessels. On the other hand, the lower center of the reflex arc where the afferent pathway ascends the sympathetic nerve or sinus nerve was situated in the medulla and from this the efferent pathway turned immediately into the efferent sympathetic fibers. Furthermore, we could notice that analysing 19 clinical cases of pulmonary edema after brain operation and brain trauma, the foci and operative attack in one group had a close relation to the higher center of the reflex arc, the preoptic areas, while in another group the foci and operative attack had a close relation to the lower center in the medulla.

The pulmonary edema could be produced, bringing about changes in the pulmonary circulation, by destroying any of the course of the pulmonary vascular
innervation. When the bilateral preoptic areas, which are regarded as the higher center of the pulmonary vascular innervation, were completely destroyed by an electrocoagulation, the pulmonary edema occurred frequently. The histology of thus produced pulmonary edema was quite similar to that of the clinical case occurred after brain lesion.

In the cases of experimentally produced pulmonary edema by complete destruction of the bilateral preoptic areas, various pathophysiological responses have been observed in detail: Respiration was markedly suppressed. Oxygen consumption and arterial blood oxygen saturation became lower. A gradual fall in arterial pressure with decreased cardiac output was seen. Pulmonary arterial pressure was elevated and reached to 50-450 mm Hg. This marked elevation of pulmonary arterial pressure was the characteristic phenomenon in the bilateral preoptic lesions. The destruction of other portions of the brain stem or the unilateral preoptic lesion did not raise pulmonary arterial pressure. Pulmonary vascular resistance increased considerably, pulmonary circulation time became prolonged, and pulmonary blood volume also seemed to be increased. Hepatic blood flow as well as renal blood flow decreased remarkably, and urine excretion became extremely low. Serum protein and colloidal osmotic pressure of plasma did not show any remarkable changes. The increase in the extracellular fluids was slight, but the fluids in the tissue stroma showed a remarkable increase due to a decreased circulating blood volume. As to the changes of electrolytes in plasma and tissues, the retention of sodium in plasma and the lung was remarkable. Tissue water was also increased in the lung. The pulmonary dilution curve which was made by an incorporation of Na24 and P32 labelled red cells showed transcapillary water exchange and the dynamics of intrapulmonary water shift clearly. Both the exudation of water into the lung and the absorption from the lung were going on rapidly and vigorously in the early stage, while in the late stage the transudation of water overwhelmed the reabsorption of water resulting in a prominent pulmonary dema. When the distribution of water to various tissues was traced by Aviado's method, the muscle reserved much water in the case of simple transfusion, while in the case of bilateral preoptic lesions, water was accumulated into the lungs selectively, producing the pulmonary edema. When Na24 was injected into the alveoli, the absorption curve of blood rose in the early stage of pulmonary edema, but at the maximal stage the absorption was suppressed producing a flat curve. The pulmonary lymphatic flow increased from time to time, but eventually it began to decrease. The reticulate fiber of the alveolar wall showed some swelling, broadening, and breaking which nicely represent the changes in the pulmonary lymphatic flow. 17-Hydrocorticosteroid in blood, 17-ketosteroid in urine and antidiuretic substance in blood increased from the beginning. It is worthy of note that these hormonal changes occurred immediately after the production of the bilateral preoptic lesions. This might indicate that the damage of the preoptic areas would influence directly upon the hormonal regulation, inducing the hormonal unbalance. VDM decreased in the liver and increased in the blood. The activity of fibrinolytic enzyme became strong, histamine of the lung tissue and free catecholamine in urine increased markedly from the beginning. The permeability of the pulmonary capillaries became increased with the lapse of time as seen in passing of the trypan blue through the pulmonary artery. Phosphatase activity, 5-nucleotidase activity, RNA metabolism, lipid metabolism and polysaccharide metabolism in the tissue of the lung and the liver became vigorous in the early stage of develop-
ment of pulmonary edema, but, as time went on they became unbalanced and weakened.

Based on the results of both clinical and experimental studies the pathogenesis of the clinical pulmonary edema occurring after a brain operation or a brain trauma was assumed to be as follows. The operation of trauma was directly responsible for the development of pulmonary hypertension, the prolongation of pulmonary circulation time, and the increase in the permeability of the pulmonary capillaries. At the same time, the operation or the trauma directly caused the changes in renal or hepatic circulation and endocrine regulation, inducing anuria, disturbance of water and electrolytes balances. The combination of these factors accelerated a selective pulmonary edema of an acute type.

Pulmonary edema occurring after an operation of cardiopulmonary diseases was often caused by a misuse of blood transfusion during and after operation. At this time something different was assumed as to the mechanism in development of the pulmonary edema. The continual rise of pulmonary arterial pressure and the remarkable lowering of colloidal osmotic pressure of plasma are the chief factors causing pulmonary edema. Once the pulmonary edema was induced, it became a stress, resulting indirectly in renal circulatory failure, discrepancy of endocrine organs, increase of the permeability of pulmonary capillaries and the further promotion of the pulmonary edema.

Pulmonary edema occurring after an operation of abdominal diseases with metabolic disorder was characteristically caused by a tremendous increase of permeability of the pulmonary capillaries.

The Mechanism of the Development of Acute Pulmonary Edema in Lung Surgery

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According to clinical observation, pathogenesis of acute postoperative pulmonary edema in lung surgery can be roughly classified into two categories. One is ventilatory insufficiency and the other is severe hemorrhage, excessive transfusion and infusion.

We gave these causative factors to dogs as experimental loads, and observed the mechanism of transudation from pulmonary blood vessels. The results were presented at the 3rd Meeting of Asian-Pacific Congress of Cardiology. Since acute pulmonary edema is a result of unbalance between transudation of blood component and absorption of the transudate, it is necessary for the study of acute pulmonary edema to demonstrate how the absorption of transudate occurs when experimental animals are exposed to these causative factors of acute pulmonary edema.

Since there is no other practical way to demonstrate directly where and how blood component enters into pulmonary blood vessels from surrounding lung interstitium, we studied the absorptive capacity of pulmonary blood and lymph vessels for transudate by observing how saline solution added with P³² as a tracer and instilled into alveoli can be transported from outside to inside of vessels. One or