SOME ASPECTS OF THE PATHOGENESIS OF EDEMA OF THE LUNGS DUE TO SILVER NITRATE

Communication III. The Mechanism of Death of Experimental Animals

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It follows from the findings of A. M. Kotovshchikov [3], who made a special study of the mechanism of development of edema of the lungs following injections of $AgNO_3$, and also from several other investigations [1, 2, 4], that after injection of $AgNO_3$ severe circulatory disturbances are often observed in addition to edema. Our researches showed that the circulatory disturbances after intravenous injections of silver are caused by spasm of the vessels of the lesser circulation. The circulatory changes, however, are not the principal mechanism of the pulmonary edema, but constitute rather a process running parallel to the edema.

Accordingly, it was considered of interest to ascertain the main cause of death after injection of $AgNO_3$ – the edema of the lungs or the circulatory disturbances arising as the direct result of the action of this compound. The present communication is devoted to the elucidation of this problem.

EXPERIMENTAL METHOD

Experiments were carried out on adult dogs of both sexes, which received injections of morphine hydrochloride in a dose of 0.01 g/kg before the beginning of the experiment. In order to assess the disturbances of the circulation, recordings were made of the arterial pressure and the pressure on the arterial side of the pulmonary circulation. As an index of the circulatory disturbances, we chose the time of onset of a severe, irreversible fall in the arterial pressure. The intensity of the edema was estimated by the ratio between the weight of the lungs in their natural state and the weight of the dry residue of the lung tissue. The arterial oxygen saturation was also recorded by means of a photoelectric oxyhemometer, and tracings were also made of the respiratory movements of the chest. The moment of death of the animals was obtained from the cessation of the tracing of respiration and of the activity of the heart. An aqueous solution of $AgNO_3$ was injected intravenously in a dose of 3.2 mg/kg in 0.4% solution into 14 animals, and of 32 mg/kg in a 4% solution into 5 animals. In the analysis of the results, we calculated the arithmetic mean ($M \pm m$) and the coefficients of correlation ($r \pm m_r$). The results were regarded as significant if the following inequality was observed:

$$\frac{M_1 - M_2}{\sqrt{m_1^2 + m_2^2}} > 3 \text{ or } \frac{r}{m_r} > 3.$$

EXPERIMENTAL RESULTS

The circulatory disturbances in the experiments in which $AgNO_3$ was injected in a dose of 3.2 mg/kg were uniform in type, and consisted in particular of the inadequate influx of blood into the systemic circulation. After definite intervals of time from the moment of injection of the preparation, the arterial pressure began to fall (Table 1).

A direct, statistically significant connection was found between the time of development of a persistent fall of blood pressure, indicating the onset of serious disturbances of the systemic circulation (circulatory anoxia), and the length of survival of the animals (see Table 1).

Observations on the oxygen saturation of the arterial blood after injection of $AgNO_3$ showed that, initially, the saturation was maintained at figures close to the original level, after which a gradual fall took place. The degree of fall of the oxygen saturation of the blood varied in different experiments, and was definitely related to the length of survival of the animals after injection of the $AgNO_3$.

It will be seen from Table 1 that a direct, statistically significant correlation was present between the degree of the fall in the oxygen saturation of the arterial blood, due to the presence or absence of anoxic anoxia, and the length of survival of the animals after the injection of $AgNO_3$. In other words, the duration of survival of the animals was not decreased in those cases

TABLE 1. Certain Indices Characterizing the Injection of $AgNO_3$ in a Dose of 3.2 mg/kg

Experiment	Time (min) between $AgNO_3$ injection and beginning of arterial pressure fall	Magnitude of O_2 saturation fall, arterial blood (conventional units)	Dry residue of lung tissue (in %)	Duration of animals' survival (min) after $AgNO_3$ injection
	I	II	III	IV
1	4.5	7.4	14.88	12
2	2.0	8.5	14.05	13
3	7.0	9.2	12.37	16
4	6.5	8.6	15.05	22
5	12.0	10.0	13.70	22
6	10.0	11.2	12.80	25
7	2.0	15.8	9.90	25
8	9.0	14.2	15.60	25
9	14.0	12.2	14.06	27
10	2.0	9.6	13.11	27
11	17.0	11.4	10.55	28
12	14.0	10.3	13.24	28
13	15.0	12.4	10.87	29
14	13.0	12.6	12.43	30
Arithmetric mean (M ± m)	9.1±1.38	10.9±0.63	13.00±0.46	23.5±1.57

Note. Coefficient of correlation for I and IV $r_1 = 0.65 \pm 0.17$; for II and IV $r_2 = 0.64 \pm 0.016$; for III and IV $r_3 = -0.36 \pm 0.23$; for I and II $r_4 = 0.24 \pm 0.25$.

in which the oxygen content of the arterial blood was low.

From the post-mortem findings, the changes in the lungs formed a perfectly uniform pattern, characterized by marked edema and severe hyperemia.

The data shown in Table 1 demonstrate that no regular connection exists between the duration of survival of the animals after injection of $AgNO_3$ and the intensity of the edema. An inverse, but not statistically significant, correlation was found between the duration of survival of the animals and the dry residue of lung tissue. No causal connection was established in our experiments between the intensity of the edema and death of the animal.

A tenfold increase in the dose of the $AgNO_3$ injected (32 mg/kg) led to a still more rapid disturbance of the systemic circulation, by comparison with the experiments in which a dose of 3.2 mg/kg was given (the difference was statistically significant; cf. Tables 1 and 2).

The kymograms show that when the larger dose of the preparation was injected, the fall of arterial pressure came on quickly (Fig. 1); with the smaller dose (Fig. 2) no significant changes in the arterial pressure had taken place after the same interval of time.

The survival period of the dogs after injection of $AgNO_3$ and the ratio between the weight of the lungs and of their dry residue differed (statistically significantly) from the corresponding indices in the previous series of experiments (cf. Tables 1 and 2). The oxygen saturation of the arterial blood was also slightly higher (the difference was not statistically significant).

As it was pointed out above, after the intravenous injection of $AgNO_3$, two fundamentally independent pathological processes develop: edema of the lungs and circulatory disturbances caused by spasm of the vessels of the lesser circulation. Both the edema of the lungs and the circulatory disorders could have been the cause of death. In the first case, it is a matter of death as the result of anoxia of an anoxic character, in the second, of anoxia of a circulatory character; in these conditions the inadequate oxygen saturation of the arterial blood could have a significant effect on the hemodynamics, but the circulatory disturbances themselves did not essentially affect the process of saturation of the blood in the lungs with oxygen.

The inverse correlation between the duration of survival of the animals and the oxygen saturation of the arterial blood is undoubtedly evidence against the fundamental role of anoxic anoxia itself in the mechanism of death of the experimental animals. The hemodynamic disturbances of the systemic circulation, arising in consequence of anoxic anoxia, also could not be a fundamental link in the mechanism of death, since a

direct, but statistically insignificant, correlation was found between the time of development of an uncompensated fall in the arterial pressure and the magnitude of the fall in the oxygen saturation of the blood; this demonstrates the absence in this case of a relationship between the onset of the fall in the arterial pressure and the oxygen content of the arterial blood. It might have been assumed that a comparatively small fall in the percentage of oxygen saturation of the arterial blood leads rapidly to considerable circulatory disturbances. Experiments in which the more severe manifestations of anoxic anoxia failed to cause such a rapid disturbance of the circulation, however, are contrary to the acceptance of such a mechanism of the circulatory disturbances.

The rejection of a leading role of anoxic anoxia in the mechanism of death still does not imply acceptance of circulatory anoxia, resulting directly from disturb-

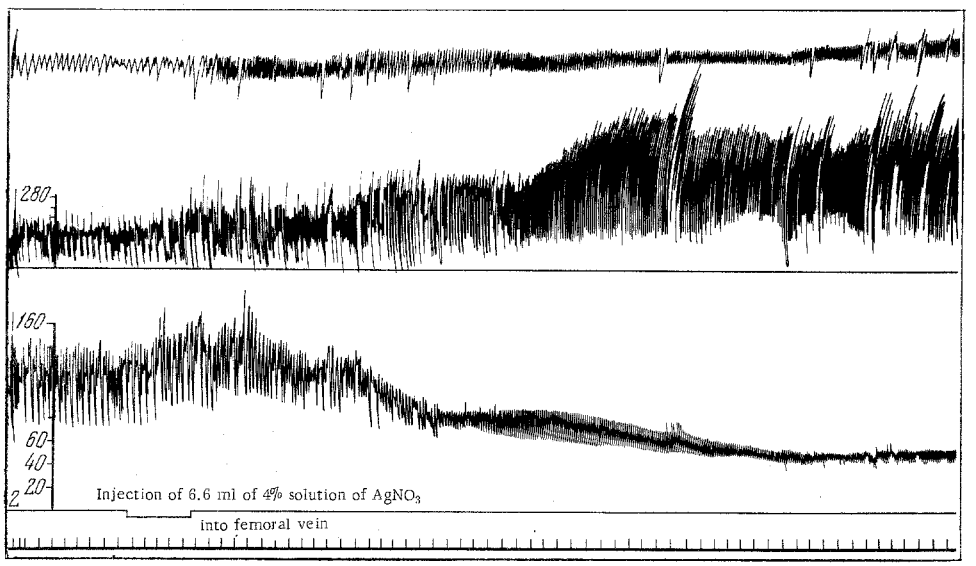

Fig. 1. The effect of intravenous injection of silver nitrate solution (6.6 ml of a 4% solution) on the respiration and blood pressure. Experiment No. 19. Male dog weighing 8.2 kg. Dose of $AgNO_3$ injected, 32 mg/kg. Significance of the curves (from above down): respiratory movements of the chest; pressure inside the right ventricle of the heart (scale in mm H_2O); pressure in the common carotid artery (scale in mm Hg); signal line; time marker – 5 seconds.

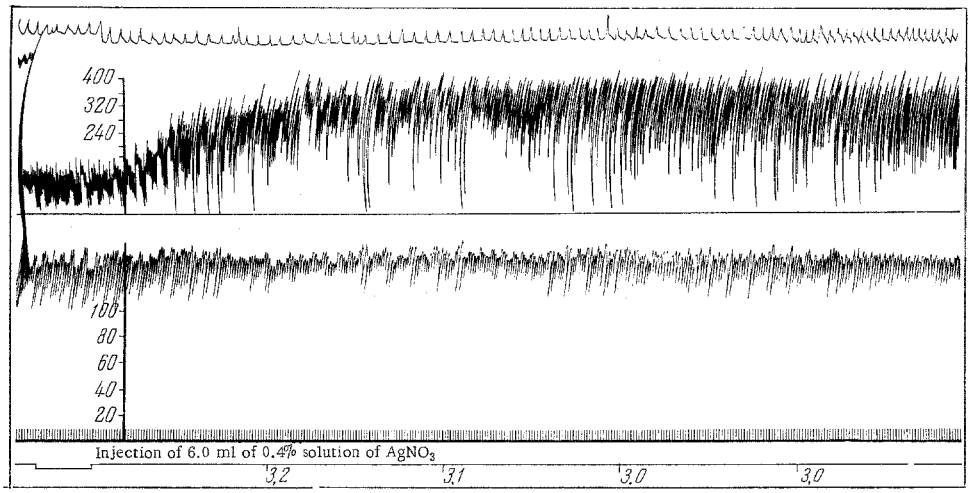

Fig. 2. The effect of intravenous injection of silver nitrate solution (6 ml of 0.4% solution) on the respiration and blood pressure. Experiment No. 4. Male dog weighing 7.5 kg. Dose of preparation injected, 3.2 mg/kg. Significance of the curves (from above down): respiratory movements of the chest; pressure inside the right ventricle of the heart (scale in mm H_2O); pressure in the common carotid artery (scale in mm Hg); time marker – 1 second; signal line.

TABLE 2. Certain Indices Appertaining to the Injection of $AgNO_3$ in a Dose of 32 mg/kg

Experiment	Time (in minutes) elapsing between moment of injection of $AgNO_3$ and beginning of fall in arterial pressure	Magnitude of fall in oxygen saturation of arterial blood (in conventional units)	Dry residue of lung tissue (in %)	Duration of survival of animals (in minutes) after injection of $AgNO_3$
15	1	6.4	18.87	9
16	2	7.6	21.07	10
17	4	8.8	16.55	12
18	3	8.0	17.98	13
19	3	14.0	17.51	18
Arithmetic mean (M ± m)	2.6 ± 0.41	8.95 ± 1.32	18.4 ± 0.77	12.4 ± 1.56

ance of the circulation by the action of $AgNO_3$ on the vessels of the lesser circulation, as the principal cause of death. However, the presence of a direct connection between the onset of the circulatory disturbances and the duration of survival of the animals makes such a point of view appear highly probable.

Injection of a large dose of $AgNO_3$ (32 mg/kg) led to the earlier death of the animals in association with very rapidly developing circulatory disturbances and a lower intensity of edema; this also is evidence against the leading role of edema of the lungs in the mechanism of death, and directly demonstrates the importance of the circulatory disturbances in this respect.

When the dose of $AgNO_3$ is increased, the relative importance of the circulatory disturbances caused directly by the silver nitrate in the mechanism of death of the animals also increases considerably. The principal pathogenetic mechanism responsible for death of the experimental animals is thus the circulatory anoxia associated with the action of $AgNO_3$ on the circulatory system.

SUMMARY

The mechanism of death was studied while investigating the pathogenesis of pulmonary edema induced by intravenous injections of silver nitrate. Hemodynamic and some other indices were recorded. A direct relationship exists between the life span following $AgNO_3$ injection and hemodynamic disturbances. There was an inverse correlation between the length of life and the oxygen content in the arterial blood. Observations presented show that the death of the animals was caused chiefly by the circulatory hypoxia induced by primary changes in the circulatory system resulting directly from the action of silver nitrate.

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