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The cause of serum anaphylactic shock and some methods of alleviating it.

By **JOHN F. ANDERSON** and **W. H. SCHULTZ.**

[*From the Hygienic Laboratory, U. S. Public Health and Marine-Hospital Service, Washington, D. C.*]

Last July a series of experiments was begun to find out, if possible, the main cause of anaphylactic shock. It was already known that the phenomena were primarily respiratory, but it was not proven whether the origin of the trouble was central or peripheral. In order to clear up this point a number of guinea pigs were given artificial respiration, and their blood-pressure recorded from the carotid by means of a mercury manometer. It was proven that the cause of death is asphyxia which is peripheral in origin. Some animals died in spite of all that could be done for them while in others the symptoms were less acute and yielded to certain forms of treatment. In the more acute forms of anaphylactic shock the respiratory muscles of the chest and the diaphragm act without the lungs fulfilling their function. That the latter do not function is shown both by the slight motion of the respiratory tambour, connected with the trachea, and by the dark venous color of the carotid blood. In spite of the dyspneic movements the animal gradually dies from weak heart resulting probably from the lack of oxygen supply. In the less acute forms of shock, however, we were able to save the animals by artificial respiration, recovery being indicated by the carotid blood assuming its normal color, the blood-pressure returning to normal and instead of the spasmodic action of the diaphragm there ensued an even, rhythmic respiration. It was also noted that in those cases not yielding to artificial respiration the chest became fixed and the rhythmic action of the bellows caused no change in the position of the walls of the chest cavity.

About this time Auer and Lewis [1] published a preliminary note in the August number of the *Journal of the American Medical Association* stating that this asphyxia is due to an inspiratory immobilization of the lungs, since, as they suggest, the lungs, upon

[1] Acute Anaphylactic Death in Guinea Pigs. Its Cause and Possible Prevention; a Preliminary Note. *Jour. of the American Med. Assn.*, 1909, liii, 458.

being exposed, scarcely collapsed; they almost, indeed, fill the chest cavity. They found that the lungs are pink and float lightly on water; pieces cut off remain distended, the cut surfaces being moderately dry when pressed give up considerable air. This immobility of the lungs in a more or less inspiratory condition they think is due probably to a tetanic contraction of the musculature of the fine bronchioli and alveolar ducts, imprisoning the air in the alveolar sacs, and that a slight degree of pulmonary edema aids in the production of this pulmonary inspiratory immobility. They also show that subcutaneous doses of 0.5 to 1 mg. of atropin sulphate administered a few minutes previous to the killing dose of horse serum abolishes the pulmonary symptoms or greatly reduces them.

Thus far our work confirms their description of the pulmonary symptoms. We find that the lungs of pigs that die in from two to five minutes after injecting intravenously 0.5 c.c. of horse serum, are almost invariably pink, full of air, and the pulmonary blood vessels filled with blood so that if immediately after death the lungs be punctured with a lead pencil or probe, a copious flow of black venous blood results. The lungs if cut from the chest cavity remain distended and when squeezed much air and some liquid exude. Out of all the controls that died in from two to five minutes there was no exception to this rule. When pigs die after a longer time than five minutes, the lungs do not as a rule remain completely distended and do not always fill the chest cavity completely. It may almost be said (judging from the experiments thus far performed) that after the killing dose of serum the duration of life is more or less proportional to the amount of collapsible lung area left just before death. A pig then that lives more than five minutes can be made to live still longer by means that will be mentioned in the following paragraph.

The condition of *partial* lung immobilization can be initiated by certain drugs that are known to act upon smooth muscle. Atropin in small doses (.01 mg. per gm. of body weight) proves very serviceable in hindering the anaphylactic action of the serum. Thus far we have found chloral hydrate and adrenalin even more effective in desensitizing the lungs towards the second injection of serum. And when oxygen is given before the second serum injection, the lungs thereby being, previous to the injection, loaded

with a supply of oxygen, the animal is often able to pass over the first critical stage of anaphylactic shock, and if sufficient lung area is left, the heart not weakened, and the vaso-motor apparatus left intact so as not to incur too low a blood pressure, the animal almost invariably recovers. The tables which follow will illustrate clearly the relative value of the four methods thus far found most efficient in reducing the death rate of guinea pigs, and the advantage of artificial respiration, especially when oxygen is used.

A large number of drugs have been tried, but thus far no combination seems to equal that of oxygen, adrenalin, and chloral-urethane just before injecting the serum into the jugular vein. Aside from the greater number of pigs saved by this method it is of interest to note the difference in time intervening between the moment of injecting the serum, and that of death. In almost every case artificial respiration with oxygen prolongs the life of the animal. Next in efficiency is the administration of atropin or still better oxygen and then atropin. It is well to observe that certain pigs die, in spite of the best treatment, even though one third or more collapsible lung area be left after the injection; the blood pressure of such animals if recorded will eventually be found to be very low and it gradually gets lower and lower until the animal finally dies. The cause of this seems to be primarily cardiac in origin, the heart beats being greatly diminished in rate and force. There is also some evidence of vaso-dilation and of venous congestion. These are in brief the points which our present experiments indicate and it is left for a subsequent paper to treat more in detail the effects of various factors influencing anaphylactic shock.

In conclusion it may be said that in the light of the experiments thus far performed the cause of sudden death from serum anaphylaxis is due to asphyxia. The asphyxia is peripheral in origin, and in all probability Auer and Lewis are correct in attributing the asphyxia to tetanic contraction of the muscles of the bronchiolæ and alveolar ducts, thereby not admitting of further ventilation of the alveolæ. This condition of inspiratory immobilization may be greatly allayed and even abolished by certain drugs. Thus far with very sensitive pigs it has been possible to save with atropin sulphate about 28 per cent., with injections of chloralhydrate plus urethane and adrenalin, 41 per cent., by ad-

ministering pure oxygen, 43 per cent., and by administering pure oxygen along with chloralhydrate and adrenalin, even 66 per cent. Almost invariably the life may be prolonged, the pigs eventually dying from low blood pressure and not from acute asphyxia.

The pigs used in these experiments were sensitized by injecting intraorbitally 0.01 c.c. of horse serum. Young pigs, weighing about 300 grams, were injected with 0.5 c.c. of the same horse serum after having been sensitized about 30 days. Pigs were never used sooner than 21 days from the time of injecting the first dose of serum. All injections, except the sensitizing one of serum, of epinephrin and of atropin were made into a special canula tied in the jugular vein. The epinephrin and atropin were usually injected intraperitoneally.

TABLE I.

Atropin Sulphate 0.01 Milligram per Gram of Body Weight.

No.	Lived.[1]	No.	Controls Lived.
61	4 minutes.		
64	5 "		
66	5 "		
68	5 "		
70	4 "		
132	23 "	136	5 minutes.
135	+	150	4 "
139	140 minutes.	151	3 "
143	+	152	15–16 hours.
145	16 minutes.	153	3 minutes.
155	4 "	156	5 "
158	+	159	+
161	+	162	+
164	4 minutes.	165	4 minutes.

4 out of 14 lived.

TABLE II.

Chloralhydrate + Urethane and Epinephrin.

No.	Lived.[1]	No.	Controls Lived.[1]
107	+	115	5 minutes.
108	5 minutes.	116	4 "
109	+	117	5 "
110	5 minutes.	118	5 "
111	6 "	119	5 "
112	+	120	+
113	+	121	5 minutes.
114	5 minutes.	122	4 "
125	5 "	123	3 "
127	6 "	124	5 "
128	+	126	+
130	9 minutes.	129	6 minutes.

5 out of 12 lived. 2 out of 12 lived.

[1] The sign + in these tables indicates complete recovery, the animal being kept for observation a week or longer. The number of minutes given in the second column is the interval of time between the moment of injecting the killing dose of serum and the final gasp.

TABLE III.

Artificial Respiration with Oxygen Alone.

No.	Lived.	No.	Controls Lived.
72	+	78	+
73	+	79	3 minutes.
74	+	80	2 "
75	+	81	4 "
76	60 minutes.	82	4 "
77	+	83	3 "
84	+	89	4 "
86	35 minutes.	93	5 "
87	28 "	94	4 "
88	8 "	95	3 "
90	+	96	9 "
91	105 minutes.	97	5 "
92	31 "	99	3 "
98	64 "	101	+
100	93 "	103	+
102	16 "	104	2 minutes.
	7 out of 16 lived.		3 out of 16 lived.

TABLE IV.

Artificial Respiration with Oxygen Accompanied by Injections of Epinephrin and Chloralhydrate-Urethane Solutions.

No.	Lived.	No.	Controls Lived.
138	+	146	5 minutes.
141	+	147	4 "
142	+	148	5 "
144	+	149	3 "
154	+	152	+
157	+	156	5 minutes.
160	37 minutes.	167	+
163	+	168	4 minutes.
170	14 minutes.	169	4 "
172	+	171	5 "
174	51 minutes.	173	4 "
176	98 "	175	6 "
		177	4 "
	8 out of 12 lived.		2 out of 13 lived.

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The influence of glycerin on gastric secretion.

By **L. KAST.**

[*From the Medical Department, New York Post-Graduate Medical School.*]

If the gastric mucosa of the living dog is exposed for a short time to from one to two per cent. of glycerin in water, the gastric secretion which follows is not more intense than after water