

LATE DEATHS OCCURRING IN ACTIVE ANAPHYLAXIS

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IN a previous paper it has been shown that in the production of passive anaphylaxis in guinea-pigs by the immediate injection of antigen after anti-serum some animals recover, some die within 5–7 min., and in others death is delayed up to about 8 hours. All or nearly all show some signs of illness. It is known that late deaths may occur in active anaphylaxis, but they do not appear to have been adequately described. The object of this work was to try to produce late deaths in active anaphylaxis similar to those described in the previous paper.

Richet (1913) classifies anaphylaxis in the guinea-pig into “highly fatal anaphylaxis, with death in less than 5 min.; acute, death occurring within an hour; chronic and death much later”. The use of the word chronic is unfortunate; in speaking of anaphylaxis in the dog Richet makes it clear that he is meaning complications due to intestinal haemorrhage following anaphylaxis. We have not met with anything comparable to this in the guinea-pig.

Gay & Southard (1907) gave the following description of the symptoms of anaphylaxis in the guinea-pig. The animal “on receiving the second dose of serum intraperitoneally, shows some or all of the following symptoms, and dies, in the majority of the cases, within an hour. In from 2 to 15 min. after injection may be noted twitching of the ears or body, coughing, retching, and less frequently general muscular contraction, with ‘becking’ and rushing about the cage: after the period of irritation, paralytic symptoms intervene, the animal squats, or feebly drags itself about the cage, complains querulously, shows respiratory distress, and finally falls on its side. This comatose period may last for some time until death intervenes, or the exitus may be precipitated by violent general spasms. The heart beats for some time after the cessation of respiration. Either the irritative or the paralytic symptoms may predominate. An animal may recover after having passed through the most characteristically severe phases of both.”

Anderson (1910) also refers to the delay in the onset of symptoms after intraperitoneal injection. He says: “Occasionally in guinea-pigs not very susceptible the onset of the symptoms following an intraperitoneal injection may be delayed 30 or 40 min., but in only a few instances have I noted the onset of symptoms delayed as long as 1 hour.” Death, he says, usually occurs within 30 min. He does not give a clear description of the symptoms occurring in the delayed cases.

Weil (1917) mentions a delayed reaction as occurring most typically when the intoxicating injection is given intraperitoneally and exceptionally after

intravenous injection. He concludes "that acute shock is induced only when sufficiently large amounts of cellular antibody and of introduced antigen are suddenly brought into contact. If either of these factors be insufficient in amount, or if the contact be very gradual instead of sudden, a mild and delayed type of shock may result."

Scott (1931) refers to prolonged shock in which "the animal lies down at full length as if in deep sleep; if disturbed, it makes clumsy efforts to rise but at once falls over again. Post-mortem there may be little to note except congestion of the liver and intestine with occasional petechial haemorrhages."

That delayed symptoms, with prolonged shock, may occur has been noted by various workers, but little attention has been paid to this aspect of anaphylaxis. In the guinea-pig the occurrence of dramatic acute symptoms has completely overshadowed the less striking symptoms which may sometimes occur.

The following experiments on the production of late deaths in active anaphylaxis fall into two groups: (a) by intravenous injection of antigen, (b) by intraperitoneal injection of antigen.

(a) These experiments were based on the idea that if conditions could be arranged so that an animal had sublethal acute symptoms these might be followed by prolonged shock and late death. The sensitizing dose was always the same, namely 0.1 c.c. of horse serum given intraperitoneally. The conditions which can be varied are the period of sensitization and the amount of antigen used for the shocking dose.

Sensitizing period 5 days; shocking dose 0.1 c.c. of horse serum intravenously. Five guinea-pigs were given 0.1 c.c. of horse serum intravenously at an interval of 5 days after the sensitizing dose. They did not show the slightest sign of illness, they ran about actively immediately after the injection and exhibited no signs of later distress.

Sensitizing period 10 days; shocking dose 0.1 c.c. of horse serum intravenously. The results of this experiment are summarized in Table I.

Table I

Period of sensitization: 10 days.

Shocking dose: 0.1 c.c. of horse serum intravenously.

Guinea-pig No.	Weight g.	Symptoms		Time of death	
		Early	Late	Early	Late
229	370	Mild	—	—	—
230	350	"	—	—	—
231	320	None	—	—	—
232	320	"	—	—	—
233	400	Mild	—	—	—
262	370	"	—	—	—
263	350	Severe	—	8 min.	—
264	370	Mild	—	—	—
265	350	"	—	—	—
266	320	"	—	—	—

Ten guinea-pigs which had been sensitized 10 days previously were given 0.1 c.c. of horse serum intravenously. Two showed no symptoms, seven had

mild symptoms, and one had typical symptoms of acute anaphylactic shock and died within 8 min. The following is a description of a typical mild case (guinea-pig 229). When put on the floor after the injection it ran about and appeared quite well for the first 2 or 3 min.; it then had rather violent, repeated hiccoughs and rubbed its nose with its paws. Breathing did not appear to be embarrassed. At the seventh minute the hair began to ruffle and the animal became less lively, it stopped running about, lost interest in its surroundings and sat quietly crouched up in a corner. At the end of half an hour it seemed quite well, its hair was normal and it ran about the floor again if disturbed.

The first five of these animals which recovered were killed by a blow on the head about 4 hours after the injection of horse serum to see if there were any gross changes in any of the organs. A few small haemorrhages, such as are found after acute anaphylaxis, were present in the lungs of Nos. 229, 230, 231 and 233. Small haemorrhages were found in the stomach in Nos. 229, 232 and 233. Otherwise all the organs appeared normal.

Guinea-pig 263 died of acute anaphylaxis, and post-mortem showed emphysematous lungs with a few small haemorrhages. The intestines were normal.

Sensitizing period 15 days; shocking dose 0.1 c.c. horse serum intravenously. The results of this experiment are summarized in Table II.

Table II

Period of sensitization: 15 days.
Shocking dose: 0.1 c.c. of horse serum intravenously.

Guinea-pig No.	Weight g.	Symptoms		Time of death in min.	
		Early	Late	Early	Late
234	420	Severe	—	8½	—
235	400	„	—	5½	—
236	420	„	Mild	—	Survived
237	410	„	—	4	—
238	450	„	—	7	—
267	320	„	—	8½	—
268	350	„	Mild	—	Survived
269	380	„	—	5½	—
270	350	„	—	6¾	—
271	350	„	—	4¾	—

Ten guinea-pigs which had been sensitized 15 days previously were given 0.1 c.c. of horse serum intravenously. Eight died of acute anaphylaxis in from 4 to 8½ min. Two animals survived. Both had severe acute symptoms, with respiratory distress and seemed likely to die, but respiration became easier after about 5 min. and the animals settled down in a corner of the cage, huddled up with hair ruffled, and remained in that state for about an hour when they again began to take interest in their surroundings.

Sensitizing period 15 days; shocking dose 0.05 c.c. of horse serum intravenously. The results of this experiment are summarized in Table III.

Table III

Period of sensitization: 15 days.

Shocking dose: 0.05 c.c. of horse serum intravenously.

Guinea-pig No.	Weight g.	Symptoms		Time of death	
		Early	Late	Early	Late
239	400	Mild	—	Survived	
240	420	Severe	Severe	—	3 hr.
241	420	„	—	7 min.	—
242	470	„	Severe	—	20 min.
243	420	Mild	Mild	Survived	
272	400	Severe	—	13 min.	—
273	400	„	—	4½ min.	—
274	350	„	Mild	Survived	
275	350	„	—	7¾ min.	—
276	370	„	—	3¾ min.	—
289	320	„	—	10½ min.	—
290	320	„	Mild	Survived	
291	330	„	—	12 min.	—
292	320	Mild	Mild	Survived	
293	380	Severe	„	„	

Fifteen guinea-pigs which had been sensitized 15 days previously were given 0.05 c.c. of horse serum intravenously. Six animals survived, and all except one had severe acute symptoms which passed on to the late signs as described in the last section. Three of these (Nos. 290, 292 and 293) were killed in from 2 to 4 hours after the injection, and in addition to the usual small haemorrhages in the lungs, there was definite congestion of the intestine, especially of the caecum, and small haemorrhages in the stomach in two of the cases. Seven of the animals died in from 4 to 13 min. after the injection. In Nos. 272, 289 and 272 there was early but quite definite vascular engorgement of the intestines, especially of the caecum. Two of the animals died later at 20 min. and 3 hours respectively. In No. 242 which survived 20 min. there was vascular engorgement of the intestine, in No. 240 the stomach had ruptured and part of its contents been liberated into the upper part of the abdominal cavity. On careful washing the stomach was seen to be haemorrhagic and there was a large ragged tear on the anterior wall. The whole of the small and large intestine was congested. The lungs were collapsed and had a few small haemorrhages in them.

(b) In the second group of experiments the shocking dose of serum was given intraperitoneally. Five guinea-pigs which had been sensitized 15 days previously were given 1 c.c. of horse serum intraperitoneally and showed no symptoms. Ten other guinea-pigs were given 3 c.c. intraperitoneally and the results are summarized in Table IV. Four out of the ten guinea-pigs died between 60 and 70 min. after the shocking dose. There were no early deaths. Two of the animals had no signs of illness, and when killed the following day nothing abnormal was found. Only three guinea-pigs showed respiratory distress, which came on later than the respiratory distress which follows the intravenous injection of antigen; in the latter case symptoms usually occur immediately and death within 7-10 min. Following intraperitoneal injection

the onset of symptoms was delayed to the seventh or fifteenth minute and the symptoms were mild. These were, however, followed by collapse and grave late signs. In the four animals which died the post-mortem appearances were similar in each case. The lungs were collapsed and occasional small haemorrhages present, and the whole of the alimentary canal from the stomach to the

Table IV

Shocking dose: 3.0 c.c. of horse serum intraperitoneally.

Guinea-pig No.	Weight g.	Symptoms		Time of death in min.	
		Early	Late	Early	Late
Period of sensitization 14 days					
294	350	None		Survived	
295	310				
296	320	Mild	"	—	60
297	330	—	"	—	70
298	330	Mild	Mild	Survived	
Period of sensitization 17 days					
284	420	—	Severe	—	65
285	450	Mild	"	—	65
286	450	—	"	Survived	
287	350	—	"		
288	370	—	"		

colon was very congested especially the caecum, which in some cases was of a purplish colour and appeared haemorrhagic. Small haemorrhages could be seen through the wall of the stomach, and on opening that organ haemorrhages were found in the mucous membrane and blood in the stomach.

The animals which survived were killed the following day, and in those which had shown severe late symptoms small haemorrhages were found in the stomach but the rest of the alimentary tract appeared to be normal.

Five normal guinea-pigs which received 3 c.c. of horse serum intraperitoneally had no symptoms. Normal guinea-pigs will tolerate larger quantities than this without any reaction.

DISCUSSION

A consideration of Table V shows that when sensitized guinea-pigs were given 3 c.c. of horse serum intraperitoneally four out of ten were killed: they

Table V. *Summary of experiments*

Sensitizing period days	Horse serum injected	No. of experiments	Guinea-pigs killed	
			Early	Late
10	0.1 c.c. i.v.	10	1	0
15	0.1 c.c. i.v.	10	8	0
15	0.05 c.c. i.v.	15	7	2
14	3 c.c. i.p.	5	0	2
17	3 c.c. i.p.	5	0	2

died late of delayed anaphylaxis. When the intravenous route was used 0.1 c.c. of horse serum killed eight out of ten animals and they died early of acute

anaphylaxis; where the dose of horse serum was diminished to 0.05 c.c. nine out of fifteen guinea-pigs were killed, of these two died late of delayed anaphylaxis. This suggests that when given intravenously the violence of the reaction depends on the amount of antigen injected. On the other hand, when given intraperitoneally another factor, namely, the rate of absorption, is introduced. When working with minimal amounts of antigen given intravenously some of the animals died of acute symptoms, death being due to respiratory failure; in some the respiratory disturbance is not so great as to cause death, and the symptoms pass off to be succeeded by others, associated with an engorgement of the portal vessels, sometimes culminating in death. These late symptoms and the associated post-mortem appearances have not been generally recognized because larger doses of antigen than were employed in these experiments kill guinea-pigs rapidly before the delayed symptoms can develop. With guinea-pigs sensitized for over 15 days larger doses produce approximately 100 per cent of acute deaths. The late manifestations show that the difference between anaphylaxis in the guinea-pig and in other animals, the dog for instance, is not so marked as text-book descriptions suggest, in fact they bring a unity into the anaphylactic picture which is absent without their recognition.

SUMMARY

Conditions are described under which late death from active anaphylaxis occurred in the guinea-pig. The post-mortem appearances were those of gastrointestinal congestion and haemorrhage resembling the changes seen in dogs dying of anaphylactic shock.

Late deaths can be produced by the intravenous injection of antigen but more easily by intraperitoneal injections.

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