THE PATHOGENESIS OF HISTAMINE SHOCK

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During the last 50 years great attention has been paid to histamine, which plays an important part in physiological and pathological processes. The administration of large amounts of histamine causes a fall in the arterial pressure (histamine shock), and this, according to popular view, arises as a result of the direct action of histamine on the capillary endothelium [10, 16, 17]. This point of view of the nature of histamine shock leaves unanswered the question of the role of histamine as a reflex stimulus. Meanwhile, facts have been discovered which are incompatible with the notion of histamine shock as the result of purely the direct injury to the capillaries [4, 7, 11, 12].

By making use of the early period of resuscitation after clinical death (as an experimental model) of an animal in which the functional state of the central nervous system has been sharply modified [2, 3, 5, 6, 8, 9, 15], we investigated the effect of injection of shock-producing doses of histamine at different periods of restoration of the vital functions on the trend of recovery of the arterial pressure during resuscitation.

METHOD

Experiments were carried out on cats of both sexes. Clinical death was induced by bleeding. To prevent coagulation of the blood, heparin "Richter" was injected in a dose of 200 units/kg. From 4 to 5 minutes after the last agonal gasp, resuscitation was instituted by V. A. Negovskii's method, but without the addition of glucose and, in the great majority of cases, without adrenalin. Histamine was injected at different periods of resuscitation subcutaneously, in the animal's forelimb, in a dose of 0.23 ml of a 1% solution per kg body weight. The experimental animals were divided into 3 groups. The first group (10 cats) received histamine at the beginning of recovery of the functions of the bulbar division of the brain, when the arterial pressure had been restored, but the function of the respiratory center was still absent. In the next group (10 cats) histamine was injected after the development of spontaneous respiration of agonal type, and in the third group (10 cats) after further restoration of the brain functions, when the respiration had acquired a periodic character.

RESULTS

The administration of histamine to resuscitated cats in the period of artificial respiration, after restoration of the function of the vasomotor center, caused practically no pressor stage of the reaction. The subsequent sharp fall in the arterial pressure characteristic of histamine shock in healthy animals was not observed in this series of experiments (Fig. 1). The injection of histamine immediately after the appearance of spontaneous respiration of agonal type led, in a considerable proportion of the experiments, at first to an obvious rise, and then to a sharp fall in the arterial pressure (Fig. 2); this fall, however, developed less rapidly and was less pronounced than in the case of depression of the arterial pressure in healthy animals receiving the same dose of histamine. The changes in the arterial pressure when histamine was injected after the development of periodic respiration were characterized by a very slight pressor effect, giving way to an ill-defined depression of the arterial pressure (Fig. 3). The mean results are given in Table 1.

One hour after resuscitation the arterial pressure in the animals was still not fully restored, irrespective of the time of injection of the histamine; its level was lower than the initial value (before exsanguination) by an amount 26-28% greater than in the resuscitated animals not receiving histamine (see Table 1).

The experiments confirmed the data relating to the increased resistance to histamine of animals resuscitated after clinical death [5], and also our own findings concerning the relationship between the appearance of a reaction to histamine and the degree of restoration of the brain functions [13]. It was characteristic that the injection of histamine in early periods of resuscitation led, despite the insignificant reaction, to the subsequent (1 hour after resuscitation) manifest delay in the normalization of the arterial pressure. This prompts the question of the state of the histamine – histaminase system at this period of restoration of the vital functions after clinical death – a system which is connected, in particular, with the level of secretion of the corticoids, for we know that the adrenal cortical hormones diminish the

sensitivity of the body to histamine [20, 21] by their influence on the activity of the enzyme histaminase [18, 19].

In order to study the role of the corticoids in the pattern of restoration of the arterial pressure of the resuscitated animal receiving histamine, we conducted special experiments.

Bilateral adrenalectomy was performed on cats in sterile conditions. In the first series of experiments (30 cats), 17-18 hours had elapsed after operation; in the second series (30 cats), the animals had received cortisone (10 mg/kg once a day) for three days after adrenalectomy. The last injection of cortisone was given 24 hours before the experiment. The mineral balance and nutrition were maintained by the introduction of milk and a salt mixture through a tube. The experiments were thus carried out on the animals 4 days after adrenalectomy; this diminished the consequences of trauma due to the operation. Resuscitated, adrenalectomized animals of the two series, together with the resuscitated animals with intact adrenals from the experiments described above, were divided into three groups in accordance with the period of administration of histamine (10 cats in each group).

The experiments confirmed our previous findings [14] that adrenalectomy does not intensify the initial phase of the reaction to histamine in animals in early periods of restoration of the vital functions after clinical death; this applied particularly clearly to the period of artificial respiration (Table 2).

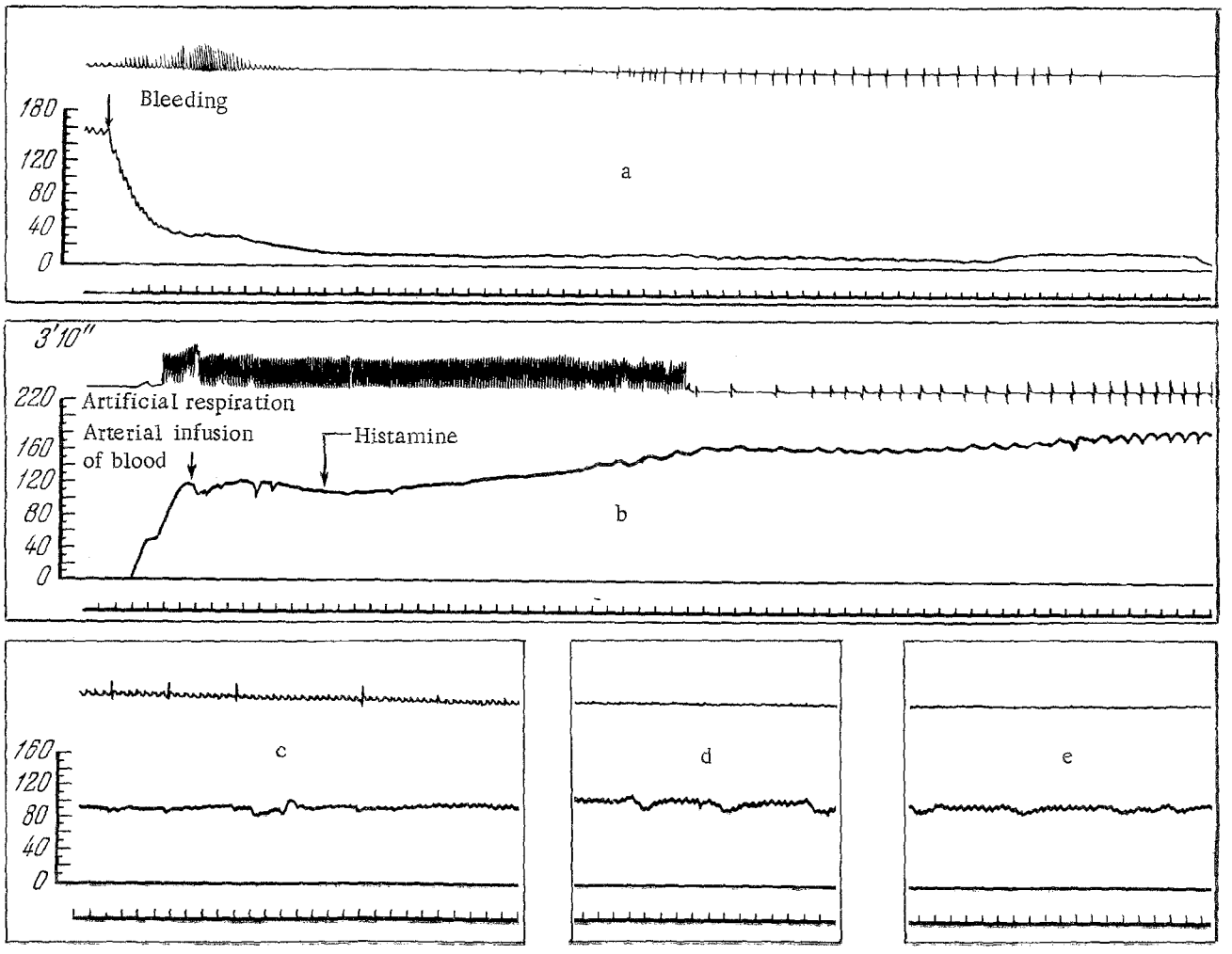

Fig. 1. Reaction of a resuscitated animal (cat, weight 2.45 kg) to histamine (2.3 mg/kg), injected before the development of spontaneous respiration (artificial respiration). a) Bleeding, onset of clinical death; b) beginning of resuscitation; c) 27 min 40 sec after beginning of resuscitation; d) 45 min after; e) 63 min 40 sec after. Significance of the curves (from above down): respiration, arterial pressure, zero line, time marker (10 seconds).

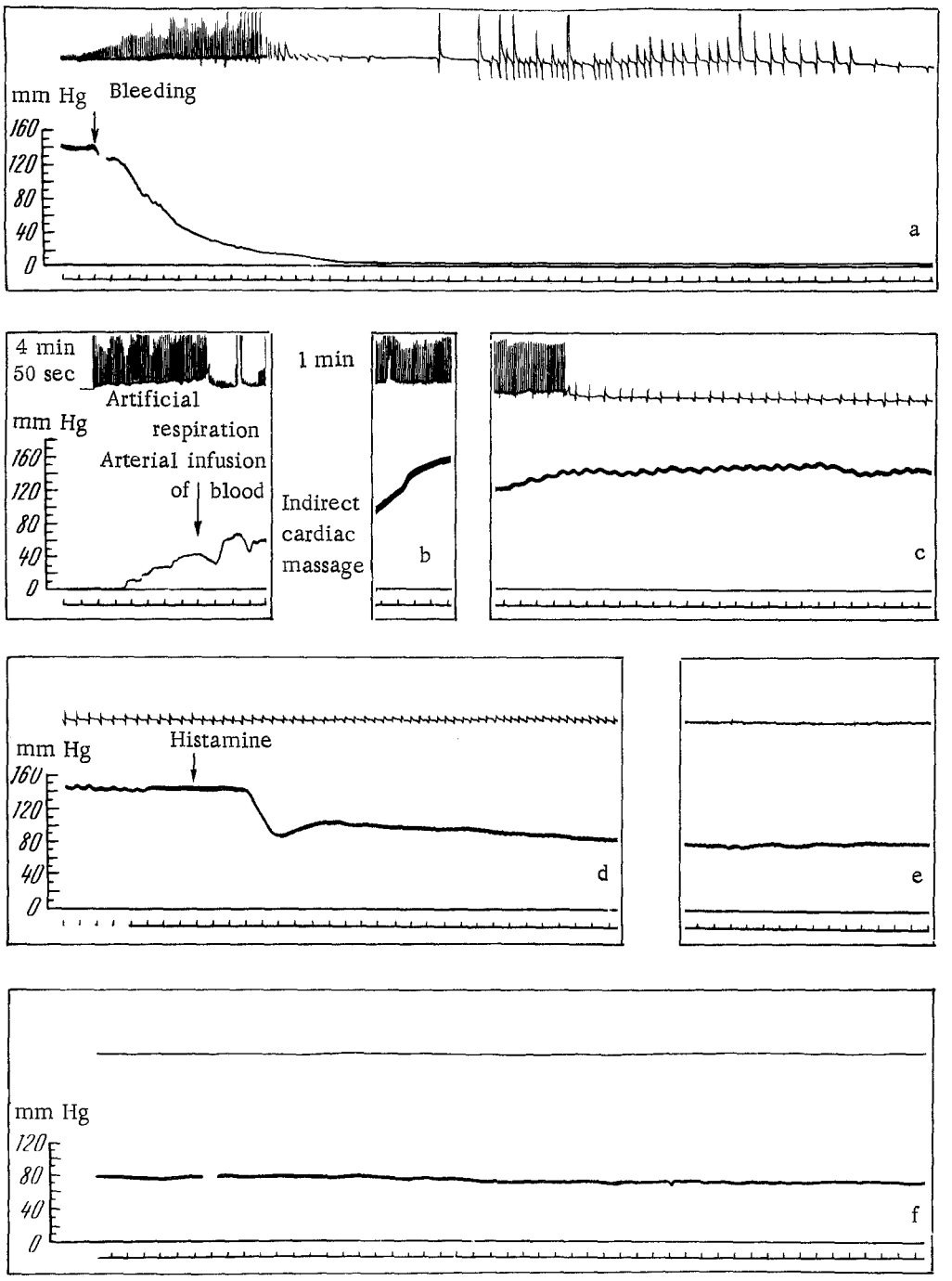

Fig. 2. Reaction of a resuscitated animal (cat, weighing 2.3 kg) to histamine (2.3 mg/kg), injected after the development of spontaneous respiration of agonal type. a) Bleeding, onset of clinical death; b) beginning of resuscitation; c) 17 min 30 sec after beginning of resuscitation; d) after 27 min 42 sec; e) after 55 min 30 sec; f) after 73 min 10 sec. Significance of the curves as in Fig. 1.

It can be seen from Table 2 that the administration of histamine in the early period of resuscitation during artificial respiration led, in spite of the preliminary adrenalectomy, to a fall in the arterial pressure to 90-95% of the initial value, i.e., just as slight a fall as in the resuscitated animals with intact adrenals (see Table 1).

Preliminary removal of the adrenals also had no significant effect on the pattern of the reaction after administration of histamine in different periods of resuscitation. For instance, after the development of spontaneous respiration of agonal type (20 experiments) and of periodic respiration (20 experiments) the depression of the arterial pressure became more pronounced, but it did not reach the degree characteristic of histamine shock. The administration of histamine was, however, reflected in the pattern of restoration of the arterial pres-

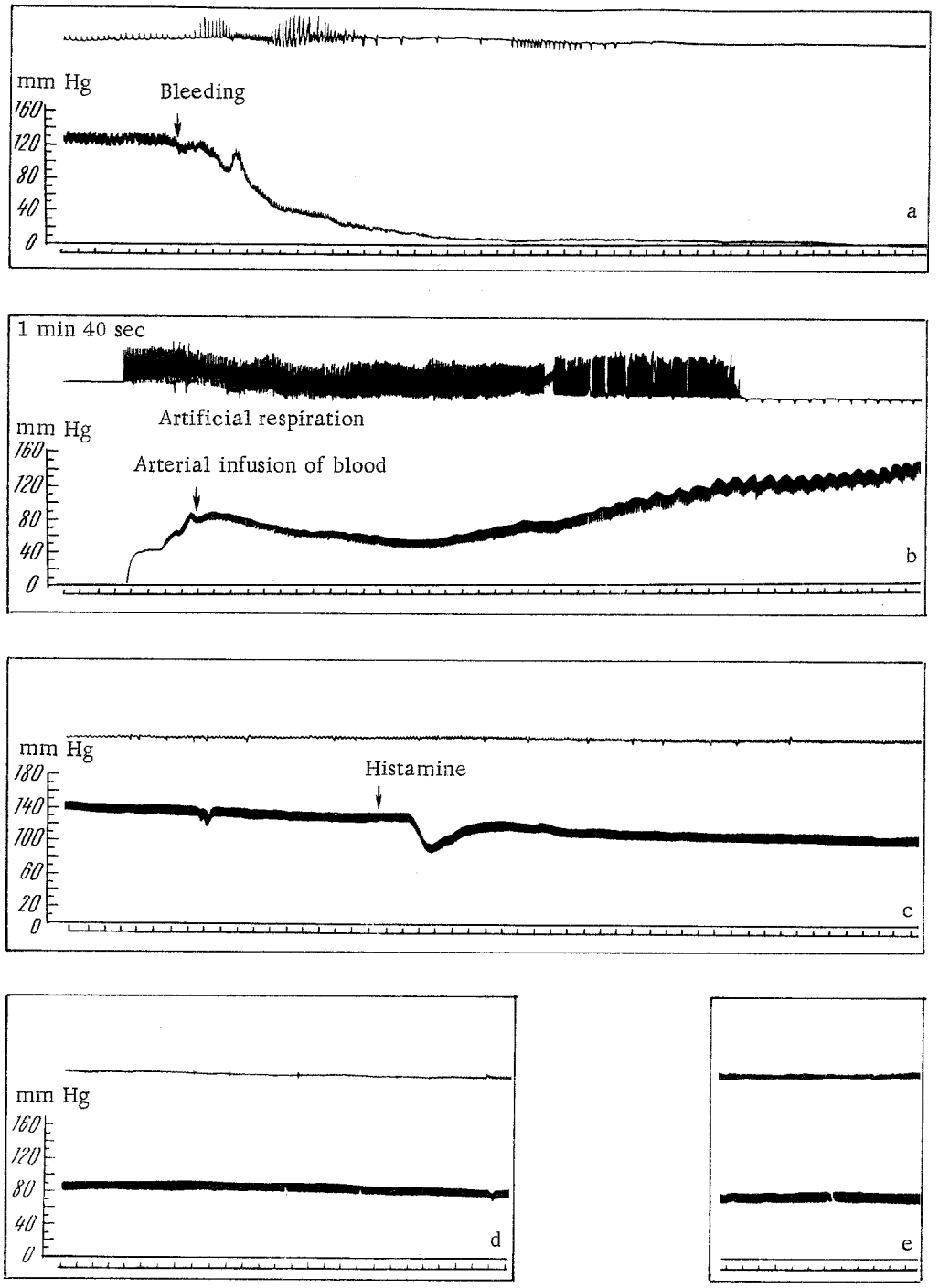

Fig. 3. Reaction of a resuscitated animal (cat, weight 2 kg) to histamine (2.3 mg/kg), injected after the development of periodic respiration. a) Bleeding and onset of clinical death; b) 8 min 10 sec after the beginning of resuscitation; c) after 32 min 20 sec; d) after 54 min 50 sec; e) after 1 hr 25 min 10 sec. Significance of the curves as in Fig. 1.

sure in the adrenalectomized animals of both series, disturbing its course and hastening the death of the animals (see Tables 2 and 3).

The duration of life and the degree of normalization of the arterial pressure of the adrenalectomized animals following administration of histamine at different periods of restoration of the vital functions after clinical death are shown in Table 3.

SUMMARY

Experiments were performed on animals revived after clinical death by V. A. Negovskii's method, with a view to studying their reaction to shock-producing doses of histamine. It appeared that in these animals the sensitivity to histamine was decreased and varied, depending on the period of brain function restoration. Histamine inhibited the normalization of arterial blood pressure in

TABLE 1. Changes in the Arterial Pressure Following Injection of Histamine at Different Periods of Restoration of the Vital Functions after Clinical Death

Character of respiration	Period of resuscitation to moment of injection of histamine: time (in min) from onset of resuscitation	Period of resuscitation to moment of injection of histamine: time (in min) from onset of spontaneous respiration	Arterial pressure: after histamine (as % of level at moment of injection) elevation to	Arterial pressure: after histamine (as % of level at moment of injection) fall to	Arterial pressure: 1 hr after resuscitation (as % of level before exsanguination)
Artificial	5	–	101	94	50
Agonal type	23	10	102	71	52
Periodic	33	20	102	75	52
Control (healthy animals)	–	–	105	58	–
Control (resuscitated animals not receiving histamine)	–	–	–	–	78

TABLE 2. Reaction of Adrenalectomized Animals, Resuscitated after Clinical Death, to Administration of Histamine during the Period of Artificial Respiration

Administration of cortisone	Resuscitation after adrenalectomy	Arterial pressure: after histamine (as % of that at the moment of injection) elevation to	Arterial pressure: after histamine (as % of that at the moment of injection) fall to	Arterial pressure: 1 hr after resuscitation (as % of level before clinical death)
–	After 17-18 hours	102	95	13
+	After 4 days	103	90	19
–	After 17-18 hours	Control (animals not receiving histamine)		40
+	After 4 days	The same		55

animals after clinical death, notwithstanding the fact that the initial phase of the action of the preparation was weak. Preliminary adrenalectomy fails to enhance the manifestations of the first (reflex) phase of histamine reaction. Another characteristic feature of the adrenalectomized animals is intensification of the second (humoral) phase, and these animals die sooner following administration of the preparation. This is evidence of the enhanced effect of the direct action of the drug on the vessels when secretion of corticoids is deficient. During the resuscitation of the animal after clinical death and in the treatment of prolonged terminal states, in view of the possible liberation of histamine as a result of the marked anoxia it is evidently desirable to administer adrenal cortical hormone preparations.

The participation of two components—reflex and humoral—in the pathogenesis of histamine shock must be recognized. The reflex component is associated with stimulation of receptors, and the humoral with the direct action of histamine on the vessels.

TABLE 3. Reaction of Adrenalectomized Animals, Resuscitated after Clinical Death, to Histamine

Administration of cortisone	Resuscitation after adrenalectomy: Time after adrenalectomy	Resuscitation after adrenalectomy: Character of respiration during injection of histamine	1 hr after resuscitation: No. of animals	1 hr after resuscitation: Arterial pressure (as % of level before clinical death)	Duration of survival after resuscitation (mean)
–	17-18 hr	Artificial	Total 10	13	1 hr 15 min
			Survived 4	33	
			Died 6	0	
+	4 days		Total 10	19	1 hr 30 min
			Survived 6	39	
			Died 4	0	
–	17-18 hr	Convulsive, agonal type	Total 10	17	1 hr 15 min
			Survived 5	33	
			Died 5	0	
+	4 days		Total 10	13	1 hr 22 min
			Survived 6	22	
			Died 4	0	
–	17-18 hr	Periodic	Total 10	9	51 min
			Survived 2	45	
			Died 8	0	
+	4 days		Total 10	18	2 hr 14 min
			Survived 6	30	
			Died 4	0	
–	17-18 hr	Control (resuscitated animals not receiving histamine)*	Total 10	40	1 hr 35 min
			Survived 10	40	
			Died –	–	
+	4 days		Total 10	55	1 hr 40 min
			Survived 10	55	
			Died –	–	

* The control series of experiments (20 animals) was conducted jointly with M. G. Kolpakov and M. G. Polyak [1].

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