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THE INHIBITION OF HISTAMINE RELEASE BY A PITUITARY-ADRENAL MECHANISM

By G. UNGAR,* *From the Oxford Extramural Unit, Research and Experiments Department, M.O.H.S., and the Nuffield Institute for Medical Research, Oxford*

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There is experimental evidence that post-traumatic mortality is reduced in guinea-pigs and rats which have undergone a previous sublethal trauma [Noble, 1943; Ungar, 1943]. It has been shown, moreover, that this resistance can be passively transferred to intact animals by the injection of the serum of traumatized animals [Ungar, 1943]. The present paper is mainly concerned with the explanation of this phenomenon while other processes of acquired resistance to 'shock' are also considered.

Methods.

The technique used throughout the experiments is based on the observation published by Gotzl & Dragstedt [1942] that blood of normal rabbits, when mixed with peptone, releases *in vitro* considerable amounts of a substance pharmacologically identifiable as histamine. This fact was confirmed and extended by using the following procedure:

Blood was collected by heart puncture from rabbits and guinea-pigs, and by section of the neck from rats; 0·5 c.c. was mixed with 1 c.c. of 0·9% solution of NaCl (*A*), and 0·5 c.c. with 1 c.c. of a 1·3% solution of peptone in saline (*B*). Coagulation was prevented with heparin or 'Liquoid Roche'. After centrifuging for 10 min., the supernatant fluid was collected and diluted to 5 c.c.

Histamine was estimated by the usual technique, guinea-pig ileum serving as test object. Unless otherwise stated, results are given in μg. of histamine dihydrochloride per c.c. of blood. The amount of histamine released is given by the difference between the two samples *A* and *B*, taking into account the direct action of peptone (*P*) on the intestine ($H = B - A - P$).

The plasma was tested without previous extraction of the histamine-like substance. This was justified by comparing the results given by six samples tested both directly and also after extraction with Code's method [1937]. The mean value of the histamine released was $0{\cdot}22 \pm 0{\cdot}08$ μg./c.c. by direct estimation and $0{\cdot}20 \pm 0{\cdot}06$ with Code's technique. In a few cases the fragment of ileum was unsuitable either because it reacted strongly to some unknown plasma constituent or because it was inhibited by peptone.

The right amount of peptone to be used, the most convenient duration for the contact between peptone and blood and the effects of temperature were investigated. As peptone is far from being a well-defined chemical product, the dose may vary from one commercial preparation to another. Duration of contact, within the limits of 10 min. to 2 hr., does not influence the results. Neither was any difference observed between mixtures kept at 18 and 38° C.

* Member of the French Scientific Mission in Great Britain.

Trauma was administered by the quantitative method described previously [Ungar, 1943] in which the amount of trauma is expressed in kg.m. of energy spent by a metal rod of known weight falling on to the thigh of the animal from a measured height.

Results were tabulated as means of several (generally eight) identical experiments. Variation of the mean was expressed in terms of the standard error (S.E.). Tests for significance of the differences were carried out by means of the t test [Fisher & Yates, 1943]. In the tables, S beside a figure indicates that there is less than 1/20 chance that this figure represents the control amount of histamine released.

Results

Histamine release in normal animals

It was confirmed that peptone releases histamine from rabbit blood *in vitro*. The average amount released in ten rabbits was $0{\cdot}58 \pm 0{\cdot}09\,\mu$g./c.c. The amount determined by Gotzl & Dragstedt on the basis of experiments on five rabbits was $0{\cdot}67 \pm 0{\cdot}12\,\mu$g./c.c. (Both these results are given in terms of histamine base.) The agreement is fairly good when allowance is made for the fact that in one case histamine estimation was done directly and in the other after extraction.

In guinea-pig blood the histamine release, although less pronounced, is still measurable and is quantitatively fairly constant. In thirty-nine adult guinea-pigs (20 ♂ and 19 ♀) the mean release was $0{\cdot}19 \pm 0{\cdot}02\,\mu$g./c.c. For males the mean release was $0{\cdot}18 \pm 0{\cdot}02$, and for females $0{\cdot}20 \pm 0{\cdot}03\,\mu$g./c.c. Ten immature guinea-pigs (each weighing less than 300 g.) gave a lower figure, $0{\cdot}13 \pm 0{\cdot}015$ μg./c.c. Although the difference between the adult and immature specimens is not significant, all subsequent experiments were performed on adult animals.

In the same conditions rat blood also releases histamine. In fourteen adult rats of both sexes the mean release was $0{\cdot}15 \pm 0{\cdot}02\,\mu$g./c.c.

Since the amount of histamine released in the blood of normal animals shows comparatively little variation, the above figures can legitimately be used for the control of experimental data.

Histamine release after injection of peptone

The object of the first series of experiments was the study of histamine release in the blood of animals which had received an injection of peptone and were therefore in a refractory state. Table 1 shows that blood taken from

Table 1. The effect of injections of peptone on the histamine release

Dose of peptone	Interval	Histamine μg./c.c.	±S.E.	No. of animals	Significance
None. Control	—	0·19	0·02	39	
500 mg./kg.	2½ hr.	0·04	0·02	8	S
,,	24 hr.	0·04	0·03	7	S
,,	48 hr.	0·03	0·015	7	S
100 mg./kg.	1 hr.	0·06	0·025	8	S
,,	20 hr.	0·11	0·02	8	S
,,	48 hr.	0·18	0·04	8	
50 mg./kg.	2 hr.	0·12	0·05	8	
10 mg./kg.	2 hr.	0·24	0·02	8	
,,	24 hr.	0·17	0·05	8	

guinea-pigs which have been given a subcutaneous injection of more than 50 mg./kg. of peptone released significantly less histamine than normal guinea-pig blood. The duration of this reduction of histamine release varies with the dose of peptone.

It may be assumed that the decrease of histamine release *in vitro* is the expression of the refractory phase which is known to follow the injection of peptone.

The effect of trauma

In order to investigate whether the resistance to trauma induced by a previous injury is a condition related to peptone refractoriness, blood of traumatized guinea-pigs was examined. Varying amounts of trauma were administered under ether anaesthesia and blood samples collected at different intervals.

TABLE 2. The effect of trauma on the histamine release

Amount of trauma	Interval	Histamine μg./c.c.	±S.E.	No. of animals	Significance
None. Control	—	0·19	0·02	39	
0·95 kg.m.	1 hr.	0·22	0·045	8	
,,	2 hr.	0·275	0·05	8	
,,	3 hr.	0·225	0·03	8	
,,	4 hr.	0·05	0·02	15	S
,,	24 hr.	0·1	0·035	7	S
,,	48 hr.	0·04	0·02	8	S
,,	3 days	0·04	0·03	7	S
,,	5 days	0·06	0·03	8	S
,,	7 days	0·04	0·01	8	S
,,	9–10 days	0·11	0·03	15	S
,,	14–15 days	0·09	0·02	12	S
,,	19 days	0·1	0·025	10	S
,,	23–24 days	0·22	0·03	9	
,,	29 days	0·27	0·04	6	
0·42 kg.m.	3 days	0·075	0·03	8	S
,,	8 days	0·11	0·03	7	S
,,	11 days	0·27	0·08	6	
0·21 kg.m.	5 hr.	0·05	0·02	8	S
,,	48 hr.	0·08	0·03	7	S
,,	4 days	0·11	0·015	7	S
,,	6 days	0·17	0·01	7	
,,	8 days	0·21	0·05	7	
0·055 kg.m.	5 hr.	0·25	0·03	8	
,,	24 hr.	0·27	0·025	8	
None. Ether anaesthesia	—	0·05	0·01	6	S
,,	1 hr.	0·16	0·015	6	
None. Haemorrhage, 1% body weight	4 hr.	0·24	0·01	7	
,,	24 hr.	0·24	0·015	8	

Results, shown in Table 2, clearly indicate that 4 hr. after trauma histamine release *in vitro* is reduced and that the reduction lasts for a period related to the amount of trauma. With a trauma of 0·95 kg.m. the return to normal requires 19–23 days, with 0·42 kg.m. 8–11 days and with 0·21 kg.m. 4–6 days. The recovery of the normal histamine release coincides with the clinical

healing of the wound. A control series of animals, submitted to ether anaesthesia but not traumatized, shows that while blood of animals under ether releases little histamine, the amount released is again normal 1 hr. later. The purpose of another control series of experiments was the study of the effect of direct blood loss. Haemorrhage amounting to 1% body weight has no effect.

Passive transfer of resistance

Table 2 shows that increased resistance to trauma, like peptone refractoriness, is accompanied by an inhibition of the histamine release *in vitro*. The next step was to examine whether this inhibition can be induced by the injection of the serum of resistant animals. In these experiments blood samples were collected 2 hr. after subcutaneous injection of sera taken, at varying intervals, from guinea-pigs which had been traumatized with 0·95 kg.m. Results of these experiments were compared with those given by the serum of animals treated with peptone or having had an anaphylactic shock. The latter guinea-pigs had been sensitized with egg albumin and 3 weeks later were tested intracardially with the antigen. All showed signs of shock but recovered and were subsequently killed and bled.

TABLE 3. Passive transfer of the inhibition of histamine release

Serum from	Dose c.c./kg.	Histamine μg./c.c.	±S.E.	No. of animals	Significance
No injection. Control	—	0·19	0·02	39	
Normal guinea-pigs	2	0·175	0·025	12	
Guinea-pigs traumatized under ether 6 hr. previously	0·001	0·06	0·02	8	S
,,	0·0001	0·17	0·02	8	
Guinea-pigs traumatized under ether 24 hr. previously	0·001	0·06	0·02	8	S
,,	0·0001	0·21	0·03	8	
Guinea-pigs traumatized under urethane 6 hr. previously	2	0·15	0·035	4	
Guinea-pigs traumatized under urethane 24 hr. previously	0·01	0·03	0·01	8	S
,,	0·001	0·19	0·04	8	
Guinea-pigs injected with 500 mg./kg. peptone 4 hr. previously	0·1	0	—	8	S
,,	0·01	0·22	0·04	8	
Guinea-pigs injected with 500 mg./kg. peptone 24 hr. previously	2	0·025	0·01	8	S
,,	0·1	0·125	0·025	8	
,,	0·01	0·175	0·02	8	
Guinea-pigs having had anaphylactic shock 3 hr. previously	0·5	0·06	0·02	8	S
,,	0·1	0·19	0·035	8	
Guinea-pigs having had anaphylactic shock 24 hr. previously	0·5	0·01	0·005	8	S
,,	0·1	0·18	0·03	8	

Table 3 shows the limit of activity of sera collected from resistant animals. Guinea-pigs injected with these sera release significantly less histamine than

normal animals or animals injected with normal guinea-pig serum. The activity of various sera shows considerable variation according to the conditions in which resistance has been acquired. For clearer understanding of the results, the activity of sera may be expressed in terms of a unit defined as the minimum dose which, when injected into normal guinea-pigs, significantly reduces the amount of histamine liberated *in vitro*. In this way, serum from normal guinea-pigs contains less than 0·5 unit/c.c., while serum from animals traumatized under ether contains between 1000 and 10,000 units/c.c. This difference may explain why peptone refractoriness cannot be passively transferred, whereas resistance to trauma can. Experience has shown that, in order to produce effective protection against peptone shock or trauma, several hundred units must be injected per kg. body weight.

Table 3 also shows that urethane tends to prevent the development of resistance. Serum of guinea-pigs traumatized under urethane is not more active than normal serum and activity develops only when the anaesthetic effect of urethane comes to an end (between 100 and 1000 units/c.c. 24 hr. after). These findings agree with other experimental facts. Subcutaneous injection of 500 mg./kg. of peptone into eight guinea-pigs under urethane anaesthesia (1 g./kg.) resulted in 100% mortality, whereas the same treatment given to unanaesthetized guinea-pigs failed to kill any. It was also shown in a previous paper [Ungar, 1943] that trauma of 3·8 kg.m. administered in specified conditions to urethanized guinea-pigs resulted in 100% mortality. The same amount of trauma given in the same conditions but under ether anaesthesia had no lethal effects.

Anaphylactic shock produces a serum of low activity. It seems certain that anaphylactic desensitization is brought about by means of a saturation of antibodies which cannot be transferred. The slight activity of sera (between 2 and 10 units/c.c.) may perhaps explain the relative protection afforded by anaphylactic shock against the effect of peptone.

The action of drugs

The next question examined was whether histamine release can be affected by drugs. All drugs were given subcutaneously, with the exception of urethane which was injected intraperitoneally.

Table 4 shows that histamine, urethane, adenosine phosphoric acid and aneurine have no effect on histamine release. Among the substances which inhibit histamine release are those that showed a definite beneficial action on post-traumatic mortality, e.g. ascorbic acid and nupercaine [Ungar, 1943]. The better results in preventing post-traumatic mortality obtained with nupercaine can now be explained by its quick and long lasting action. On the other hand, the long delay between the administration and the beginning of the action of ascorbic acid may explain certain reports of its failure to

TABLE 4. Action of drugs on the histamine release

Drug	Dose per kg.	Interval	Histamine μg./c.c.	±S.E.	No. of animals	Significance
Control	—	—	0·19	0·02	39	
Histamine HCl	2·5 mg.	3 hr.	0·165	0·03	7	
Urethane	1 g.	1 hr.	0·22	0·04	20	
,,	1 g.	24 hr.	0·19	0·05	7	
Adenosine phosphoric acid	10 mg.	3 hr.	0·19	0·02	8	
,,	10 mg.	24 hr.	0·24	0·03	7	
Aneurine	10 mg.	3 hr.	0·28	0·05	8	
Ascorbic acid	100 mg.	½ hr.	0·2	0·025	8	
,,	100 mg.	1 hr.	0·16	0·04	8	
,,	100 mg.	2 hr.	0·08	0·03	8	S
,,	100 mg.	3 hr.	0·04	0·02	8	S
,,	100 mg.	6 hr.	0·04	0·02	8	S
,,	100 mg.	13 hr.	0·06	0·03	8	S
,,	100 mg.	24 hr.	0·16	0·03	8	
,,	100 mg.	48 hr.	0·19	0·03	7	
Nupercaine HCl	4 mg.	12 min.	0·09	0·025	8	S
,,	4 mg.	½ hr.	0·04	0·02	8	S
,,	4 mg.	4½ hr.	0·1	0·03	8	S
,,	4 mg.	24 hr.	0·06	0·02	7	S
,,	4 mg.	48 hr.	0·2	0·01	7	
Procaine HCl	100 mg.	4½ hr.	0·07	0·02	8	S
,,	100 mg.	24 hr.	0·19	0·045	8	
,,	100 mg.	48 hr.	0·185	0·025	7	
Cocaine HCl	40 mg.	3 hr.	0·06	0·02	8	S
,,	40 mg.	24 hr.	0·07	0·03	8	S
Adrenaline HCl	0·1 mg.	2 hr.	0·03	0·01	8	S

protect against anaphylactic and peptone shock [Eyer, Dragstedt & Ramirez, 1938; Dragstedt, Eyer & Ramirez, 1938]. Table 4 also shows that procaine has a comparatively short action on histamine release; this may explain its inability to prevent post-traumatic mortality. As cocaine was also found active, it is possible that the power to inhibit histamine release *in vitro* is in some way related to local anaesthetic action. High, unphysiological doses of adrenaline also have an effect on histamine release.

It could be asked whether the inhibition of histamine release induced by drugs can be transferred to non-treated guinea-pigs by injecting the serum of treated animals. Serum of animals treated with ascorbic acid or nupercaine was therefore injected into normal guinea-pigs. Blood from eight guinea-pigs injected with 1 c.c./kg. of ascorbic acid serum released $0{\cdot}19 \pm 0{\cdot}02\,\mu$g./c.c. histamine. Nupercaine serum injected into eight guinea-pigs at a dose of 0·1 c.c./kg. gave a release of $0{\cdot}07 \pm 0{\cdot}02\,\mu$g./c.c. and at a dose of 0·01 c.c./kg. gave $0{\cdot}21 \pm 0{\cdot}03\,\mu$g./c.c. It seems therefore probable that ascorbic acid has a direct action since the serum of animals treated with this substance is inactive. Nupercaine, on the other hand, probably acts by producing some other substance which is contained in the serum of treated animals in amounts of 10–100 units/c.c.

The effect of adrenalectomy

The following series of experiments was designed to determine the origin of the inhibitory substance present in the serum. An attempt was first made to determine the part played by the adrenals in the production of this substance. Table 5 shows a comparison between normal rats and rats adrenalectomized 2 days previously and maintained on salt water. It is clear that

TABLE 5. Histamine release in the blood of normal and adrenalectomized rats

	Normal rats				Adrenalectomized rats			
Treatment	Histamine μg./c.c.	±S.E.	No. of animals	Significance	Histamine μg./c.c.	±S.E.	No. of animals	Significance
None. Control	0·15	0·02	14		0·27	0·07	12	
Peptone, 500 mg./kg.	0·03	0·01	8	S	0·16	0·02	8	
Trauma, 1·9 kg.m.	0·04	0·02	8	S	0·22	0·03	7	
Ascorbic acid, 100 mg./kg.	0·025	0·02	8	S	0·01	0·01	7	S
Nupercaine, 20 mg./kg.	0·03	0·01	8	S	0·21	0·035	8	
Adrenaline, 0·5 mg./kg.	0·03	0·01	8	S	0·21	0·02	8	
Adrenal cortical extract, 0·1 mg./kg.	0·025	0·01	8	S	0·03	0·02	8	S
Serum of traumatized guinea-pigs, 2 c.c./kg.	0·03	0·01	8	S	0·29	0·06	8	

normal rats, like guinea-pigs, release less histamine when subjected to peptone, trauma, ascorbic acid, nupercaine, adrenaline, adrenal cortical extract and serum of traumatized animals. Adrenalectomized rats, however, are affected only by ascorbic acid and cortical extract. The action of ascorbic acid was to be expected from the results of experiments with the serum of guinea-pigs treated with this substance. A crude cortical extract at a dose corresponding to 0·1 mg. of fresh gland inhibited the histamine release both in normal and adrenalectomized animals. However, the active substance of this extract cannot be the same as the inhibitory substance of the serum since the latter has no action in adrenalectomized animals.

The effect of adrenalectomy and hypophysectomy on the production of the inhibitory substance

While the adrenals seemed to be indispensable for the inhibition of histamine release (except in the case of ascorbic acid), the site of production of the inhibitory substance of the serum was to be found elsewhere. An obvious organ to be examined was the pituitary body. Tepperman, Engel & Long [1943], reviewing the literature of adrenal cortical hypertrophy, concluded that changes in the adrenals can only be brought about through the pituitary. In order to examine the parts played by the adrenals and pituitary in the production of the inhibitory substance, guinea-pigs were injected with serum collected from normal, adrenalectomized and hypophysectomized rats submitted 5 hr. previously to a trauma of 0·95 kg.m. Guinea-pigs injected with normal rat serum were used as controls.

Table 6 shows that serum of intact traumatized rats has an activity of the same order as that of similarly treated guinea-pigs (1000–10,000 units/c.c.). The serum of adrenalectomized and traumatized rats has the same activity.

TABLE 6. Activity of sera from normal, adrenalectomized and hypophysectomized rats after trauma

Serum from	Dose c.c./kg.	Histamine μg./c.c.	±S.E.	No. of animals	Significance
None. Control	—	0·19	0·02	39	
Normal rats	0·1	0·22	0·02	8	
Normal traumatized rats	0·001	0·03	0·01	8	S
,,	0·0001	0·16	0·02	8	
Adrenalectomized traumatized rats	0·001	0·02	0·01	8	S
,,	0·0001	0·21	0·02	8	
Hypophysectomized traumatized rats	0·1	0·2	0·025	8	

Now, according to Table 5, blood from adrenalectomized and traumatized rats releases a normal amount of histamine. This can be explained by assuming that adrenalectomy does not prevent the production of the inhibitory substance but that this substance can only act through the adrenals. On the other hand, Table 6 indicates that the inhibitory substance is not produced in the absence of the pituitary.

Effect of adrenal and pituitary extracts

Adrenal and pituitary extracts were finally tested in guinea-pigs. The results summarized in Table 7 show that both glands contain highly active products. A crude adrenal extract in saline contains 100,000–1,000,000 units/g. of fresh tissue. A crude alkaline pituitary extract has the same activity. Liver extract, tested as control, contained no active principle in 100 mg.

TABLE 7. Effect of adrenal and pituitary extracts on histamine release

Extract	Dose* per kg.	Histamine μg./c.c.	±S.E.	No. of animals	Significance
None. Control	—	0·19	0·02	39	
Guinea-pig liver	100 mg.	0·17	0·02	8	
Rat adrenal	100 mg.	0·03	0·01	8	S
Guinea-pig adrenal	1 mg.	0·02	0·005	8	S
,,	0·01 mg.	0·03	0·01	8	S
,,	0·001 mg.	0·21	0·03	8	
Whole cortical extract, Kendall	1 mg.	0·025	0·02	8	S
,,	0·1 mg.	0·19	0·05	8	
Desoxycorticosterone acetate†	2 mg.	0·19	0·02	8	
,,	10 mg.	0·19	0·035	8	
Guinea-pig pituitary	0·01 mg.	0·05	0·02	8	S
,,	0·001 mg.	0·19	0·02	8	
'Antex'†	0·1 mg.	0·04	0·01	8	S
,,	0·01 mg.	0·21	0·02	8	
'Corticotrophin'†	0·01 μg.	0·04	0·02	8	S
,,	0·001 μg.	0·23	0·03	8	

* Unless otherwise stated, doses are given in weights corresponding to fresh tissue.
† Dose given in weight of pure product.

Purified products are less active. A whole cortical extract prepared by Kendall contains between 1000 and 10,000 units/g. of fresh tissue. Synthetic desoxycorticosterone acetate is inactive. A commercial preparation of anterior pituitary ('Antex') contained only between 10,000 and 100,000 units/g. of dry substance. However, the most powerful product tested so far is a corticotrophic hormone* containing between 10^8 and 10^9 units/g. of dry substance.

The most likely explanation of the inhibition of the normal histamine release in blood *in vitro* is that after certain stimuli (tissue damage, peptone injection, administration of drugs, etc.) the pituitary releases into the circulation an active principle that stimulates the adrenals, which in their turn act directly or indirectly on the blood cells. Further investigation is necessary in order to determine the mechanism of this action more precisely.

Discussion

Liberation of histamine from isolated tissue fragments has already been used as a test for anaphylactic sensitivity and desensitization [Ungar & Parrot, 1936; Schild, 1937; Campbell & Nicoll, 1940]. Katz [1940] was the first to use blood for *in vitro* anaphylaxis. Histamine release can also be used as a test for peptone shock since Feldberg & O'Connor [1937], Dragstedt & Mead [1937] and Tinel, Ungar & Parrot [1938] have shown that peptone acts largely by releasing histamine from certain tissues. It is probable that lung tissue provides the main source of histamine in guinea-pig anaphylactic and peptone shock and that blood cells are only of secondary importance.

The fact that histamine liberation is used as a test does not imply that it is the only or even the main substance released. The reason for using histamine is that it can be detected in extremely small amounts by a comparatively easy technique.

Desensitization, which follows anaphylactic shock, is generally ascribed to the saturation of antibodies. No such explanation can be put forward to explain the refractory phase brought about by peptone. Peptone has no antigenic properties [Fink, 1919] and peptone shock therefore is not the expression of an antigen-antibody reaction. Mead, Dragstedt & Eyer [1937] and Dragstedt [1943] suggest that refractoriness is the result of the exhaustion of the histamine supply of certain cells and can therefore be brought about only after heavy shock and not at all by injection of small doses or by subcutaneous administration. If inhibition of the histamine release *in vitro* can be accepted as a criterion of refractoriness, this condition can without doubt be induced by small subcutaneous doses giving no shock and presumably no appreciable liberation of histamine. Moreover, Feldberg & O'Connor [1937] have found that in isolated and perfused lung a second injection of peptone may give rise to a higher histamine output than the first. Exhaustion of the

* I am indebted to Organon Laboratories Ltd. for generous supply of 'Corticotrophin'.

histamine supply can play some part in anaphylactic desensitization as in peptone refractoriness but just as the primary cause in the first case is the saturation of antibodies, in the second it is probably some other process.

Peptone refractoriness probably belongs to the non-specific conditions of resistance described under the name of tachyphylaxis [Champy & Gley, 1911] or skeptophylaxis [Ancel, Bouin & Lambert, 1911]. It is probably related to the phenomena described by Selye [1937] as adaptation to 'alarming' stimuli. The experiments reported in this paper may supply an explanation for the mechanisms involved in these reactions. Selye has shown that 'adaptation' is accompanied by an increase in the volume of the adrenal cortex. Tepperman *et al.* [1943] have reviewed the various conditions in which adrenal cortical hypertrophy had been observed, e.g. injection of peptone [Whitehead, 1932], exposure to excessive cold or heat, trauma, burns, starvation, muscular exercise, adrenaline, formaldehyde, etc., and they suggested that the common factor present in most cases to which the adrenals react is the presence of protein breakdown products in the circulating blood.

The experiments described in the present paper give confirmation of the part played by the adrenals and the pituitary in the non-specific protective or 'adaptative' process suggested by morphological observation. These experiments may also explain why adrenalectomized animals are highly sensitive to trauma [Freed, 1932; Swingle & Parkins, 1935; Swingle, Parkins, Taylor & Hays, 1938; Hechter, Krohn & Harris, 1942; Noble & Collip, 1942]. Increased sensitivity to various stimuli was also observed in hypophysectomized animals by Tyslowitz & Astwood [1942], Noble & Collip [1942], Joseph, Schweitzer & Gaunt [1943] and Reiss, Macleod & Golla [1943]. The latter writers have also observed that corticotrophic hormone protects animals against shock-like conditions.

The experiments described above suggest that certain stimuli bring about the secretion by the pituitary of a hormone included in the corticotrophic fraction. This hormone, through the mediation of the adrenal cortex, determines a change in the blood cells and probably other tissues which can be detected by the reduced capacity of blood cells to liberate histamine under the action of peptone. From the practical point of view the cellular change determined by the joint action of the pituitary and the adrenal cortex is beneficial to the animals which become resistant to any further action of the stimuli. The protection thus created is not specific, i.e. the refractory state created by peptone affords protection against the effects of tissue damage and *vice versa*. With certain quantitative limitations, the protective action can be transferred by injecting sera containing the active principle into animals not subjected to the original stimulus.

SUMMARY

1. Blood of normal rabbits, guinea-pigs and rats, when mixed *in vitro* with peptone, liberates histamine into the plasma. The amount of histamine released per c.c. of blood shows little variation within the same species.

2. Histamine release is significantly reduced in the blood of guinea-pigs and rats submitted to the action of peptone, trauma or certain drugs (adrenaline, local anaesthetics, ascorbic acid).

3. Inhibition of histamine release can be transmitted to normal animals by injection of the serum of traumatized animals. A unit is defined for measuring the activity of these sera.

4. Evidence is given that the inhibitory substance present in active sera is produced by the pituitary and acts through the adrenals.

5. The significance of the reaction is discussed from the point of view of peptone refractoriness, non-specific resistance and induced insensitivity to traumatic shock.

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