ENDOCRINOLOGY

THE BULLETIN OF
THE ASSOCIATION FOR THE STUDY
OF INTERNAL SECRETIONS

VOLUME 21 MARCH, 1937 NUMBER 2

STUDIES ON ADAPTATION

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In a preliminary publication (1) attention has been called to a syndrome which appears when a severe injury is inflicted upon the organism. This syndrome is independent of the nature of the damaging agent and represents rather a response to damage as such. Exposure to cold, traumatic injuries, excessive muscular exercise, spinal shock, acute infections, and intoxications with various drugs will evoke this syndrome if they damage the organism sufficiently. The course of this reaction, which we have interpreted as an expression of general defence, may be divided into three stages. During the first, or acute stage, observed in the rat ordinarily 6 to 48 hours after the initial injury, one notes a rapid decrease in the size of the thymus, spleen, lymph glands and liver; disappearance of fat tissue; edema formation, especially in the thymus and loose retroperitoneal connective tissue; accumulation of pleural and peritoneal transudate; loss of muscular tone; fall of body temperature; formation of acute erosions in the digestive tract, particularly in the stomach, small intestine and appendix; loss of cortical lipoids and chromaffin substance from the adrenals; and sometimes hyperemia of the skin, exophthalmos, increased lachrymation and salivation. In very severe cases, focal necrosis of the liver and dense clouding of the crystalline lens may be observed.

After a few days, however, a certain resistance is built up against the damaging stimulus. Thus, for instance, in the experiments in which such a syndrome was produced by means of a drug, we found that even though we continued to inject the animals daily with the same dose of the substance which originally evoked all these symptoms, the organ changes gradually disappeared, and finally the animals became resistant. If daily injections were continued still longer the animals lost their resistance, and in a third stage died with organ changes similar to those seen in the first stage. We have termed this reaction the 'general adaptation reaction' and its 3 stages the 'stage of alarm', the 'stage of resistance', and the 'stage of exhaustion'. The name 'stage of alarm' has been chosen for the acute stage because we consider

it an expression of the general alarm of the organism when first confronted with a damaging agent. Stimuli capable of evoking such a reaction of alarm will, for the sake of brevity, be referred to as 'alarming stimuli', and the dose of a drug or stimulus required to cause a typical alarm reaction will be called the 'alarming dose' of such a drug or stimulus. It is evident that in the case of injuries so severe that adaptation cannot occur, the alarm stage will be the only one to develop. In this case it is hardly possible to speak of an 'alarm stage', and the term 'alarm reaction' will therefore be used whenever we discuss this stage as a separate entity.[1] It must be borne in mind, however, that the alarm reaction may also represent the first stage of the adaptation reaction. The ability of an animal to offer resistance to damaging stimuli—that is, the ability to adapt itself—will be referred to as the 'adaptation energy'. This, as we shall see, is limited in quantity, and is drawn upon during the process of adaptation.

It seems difficult at first to understand why the organism should react to entirely different stimuli in an identical manner. The great similarity between the symptoms of the alarm reaction and those of histamine toxicosis or anaphylactic and surgical shock make it likely that the liberation of large quantities of histamine or pharmacologically similar substances (adenylic acid derivatives, acetylocholine, kallikrein) from the tissues plays an important part in producing this syndrome (2). The difference between the response to histamine and that to other drugs is that the former produces the characteristic symptoms at doses especially far from lethal and more regularly and promptly than any other drug studied. The latent period in the case of other drugs might represent the time necessary for the liberation of histamine from tissues. Further evidence in support of this hypothesis will be discussed in connection with our experiments in the following pages. The fact that histamine is a physiological constituent of tissues has been generally recognized since the classical demonstration of its presence in the spleen by Dale and his school (3). That large quantities of a histamine-like substance are liberated into the blood stream during surgical shock was made very probable by the studies of Cannon (4). In spite of the contrary opinion expressed in some more recent publications, this still seems to be the most plausible explanation for the symptoms of secondary traumatic shock. It should be stressed at the beginning, however, that there is no evidence at hand which would prove that the substance or substances produced during the alarm reaction are chemically identical with, or even allied to histamine. In order to avoid coining more new names than is necessary, I shall refer to this hypothetical metabolite or group of metabolites with histamine-like pharmacological actions as 'H-substance', following herein the example of Lewis (5), who used this term to designate the histamine-like substance formed in the skin during his 'triple-response' reaction. It should be stressed, however, that the substance acting in the skin

[1] A few months ago a publication by T. Klein (Wien. Arch. f. Inn. Med. 28: 251. 1936) appeared in which the term 'alarm reaction' is used to designate the reflex inspiration and some accompanying motor phenomena elicited by fright and other psychic stimuli. Since we have already used this term in several publications for the first stage of the adaptation reaction, it would lead to confusion if we were to change it now. One should sharply distinguish, however, between Klein's respiratory reflex and the alarm reaction in the sense in which the term is used here.

is not necessarily identical with the substance formed during the alarm reaction.

That the organ changes are not due to a direct action of the damaging agent on the various tissues, as might have been supposed in cases in which the reaction was elicited by drugs, is proved by the experiments on spinal shock, in which a relatively small lesion of the spinal cord produced changes characteristic of the alarm reaction in the various organs. The assumption of a mediator which carries the effect from the site of lesion to the various organs seems justified, therefore, even though we do not know as yet whether it is transmitted by way of the blood stream or by way of the nervous system. If the above hypothesis be correct, surgical shock would represent a special form of the alarm reaction, in which H-substance is mechanically liberated from the tissues, differing from other types of the alarm reaction only in that the latter group liberate similar substances by other means [chemical (drugs), physical (cold, x-rays, ultra-violet rays), or nervous stimuli (spinal shock)].

It would hardly be worth while to describe all the experiments in which an alarm reaction was obtained by various drugs. Suffice it to mention that an alarm reaction develops after the administration of any drug administered in sublethal doses, unless the specific pharmacological actions of the drug exert such a violent selective action on vital centers (heart, respiratory center, etc.) that death ensues as a result of this selective action before any marked general damage occurs. Among others, atropine, morphine, adrenaline, vasopressin and formaldehyde have been studied more particularly, and all these drugs produced the symptoms of the alarm reaction when given twice daily for 48 hours in sublethal doses.

ALARMING STIMULI

Groups of 10 female rats, 3 months of age, were used for each experiment in this series. They received a dose of the drug in question which had been found in preliminary experiments to be just sufficient to produce an alarm reaction; that is to say, they received the alarming dose of the drug in 4 injections within 48 hours. Four animals in each group were killed at intervals during the first 24 hours, beginning at the 8th hour after the first injection, for investigation of the acute symptoms of the alarm reaction. The remaining 6 were autopsied 48 hours after the beginning of the experiment; that is, after having received the 4 injections. The drugs used were adrenaline (0.2 cc. of a 1:1000 solution twice daily), formaldehyde (0.5 cc. of a 4 per cent solution twice daily), morphine sulphate (2 cc. of a 1 per cent solution twice daily). It would be tedious to describe in detail all autopsy observations made during the acute stage in the various groups, since the findings showed only quantitative variations and were otherwise essentially the same in each group. Edema formation in the thymus, the retroperitoneal connective tissue and the omentum, and formation of peritoneal and pleural transudates were constant findings. Occasionally hemorrhagic lung edema or hemorrhages into the urinary bladder were seen. Clouding of the crystalline lens was not observed in this series, but other experiments in which higher dosages of the same drugs were

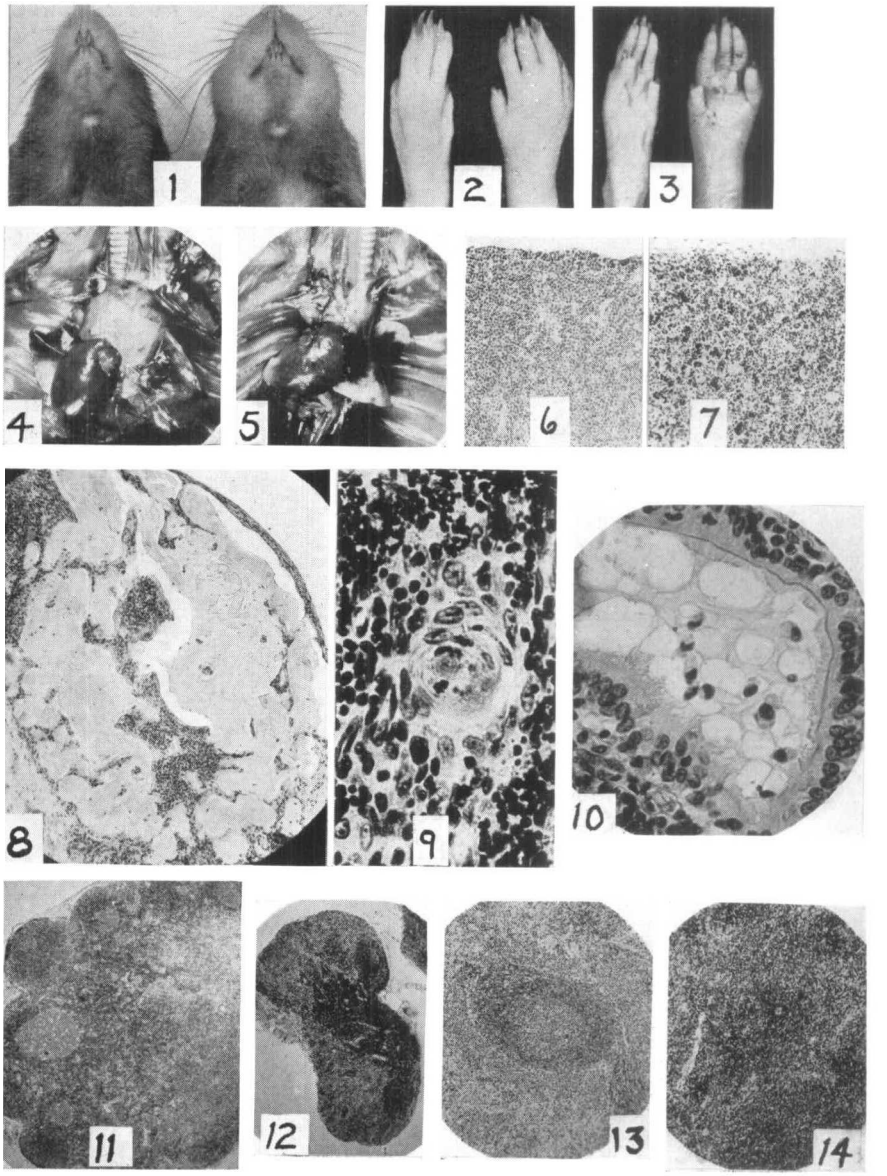

Fig. 1-14. *1, left.* Normal control rat; *right,* facial edema following injection of egg-white. *2, left.* Paw of normal control rat; *right,* edema of the paw after injection of egg-white. *3.* Same as *2,* from the plantar side. *4.* Thymus of a normal female rat in situ. *5.* Atrophic thymus of a rat in the alarm reaction (elicited by formaldehyde intoxication). *6.* Cortex of a normal rat thymus. Note the regular, normal nuclei in the thymocytes. *7.* Marked karyorrhexis and pyknosis of the thymocytes in the alarm reaction (elicited by excessive muscular exercise). *8.* Large cyst in the thymus of a rat chronically treated with estrone. Note the epithelial lining of the cyst and the dense colloid in the lumen. *9.* Giant Hassall corpuscle in the thymus of a rat in the alarm reaction (elicited by excessive muscular exercise). *10.* Cyst lined with ciliated epithelium in the thymus in the alarm reaction (elicited by surgical injury of multiple bone fractures). *11.* One of the iliac lymph glands in a normal rat. *12.* Iliac lymph glands corresponding to that shown in *11* in the alarm reaction (elicited by excessive muscular exercise). *13.* Malpighian follicle in a normal spleen. *14.* Malpighian follicle in the alarm reaction (elicited by excessive muscular exercise).

given showed that acute cataracts do develop in some cases under the influence of the non-specific damage caused by various drugs. A slight fall in body temperature (1 to 2°C.) was also characteristic during this early stage.

A summary of the most important changes in the gross weight of the

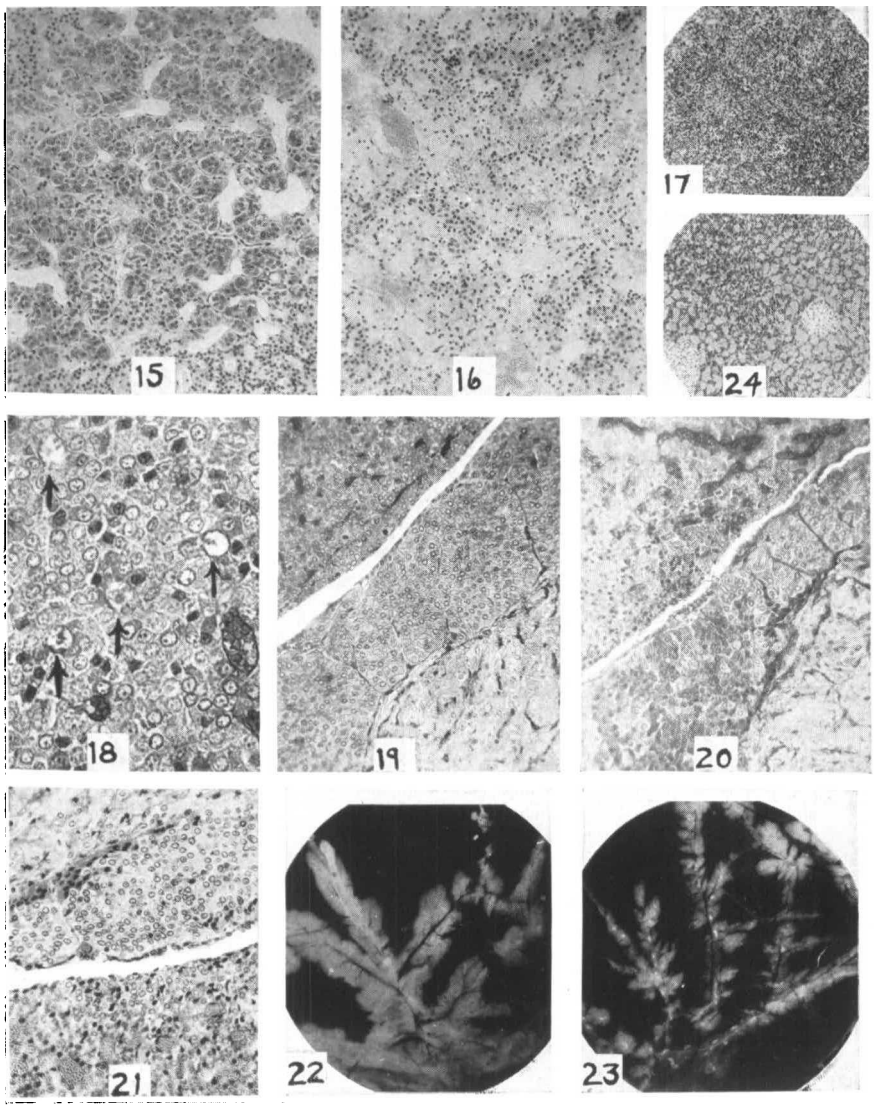

Fig. 15-24. *15.* Adrenal medulla of a normal rat. *16.* Adrenal medulla in a severe alarm reaction (elicited by excessive muscular exercise). Note the almost complete dissolution of the epithelial cells. *17.* Anterior lobe of the hypophysis in the alarm reaction (elicited by exposure to cold). Note the large number of pyknotic nuclei which appear as small black dots at this magnification. *18.* Four large 'signet-ring' cells, marked by arrows, in the alarm reaction (elicited by morphine intoxication). *19.* Hypophysis of a normal rat. Anterior lobe in lower right of the field; posterior lobe in upper left, and middle lobe between. *20.* Hypophysis in the alarm reaction (elicited by excessive muscular exercise). Note numerous necrotic cells throughout the middle lobe. *21.* Hypophysis in the alarm reaction (elicited by exposure to cold). Note the characteristic disintegration of middle lobe cells along the borderline between the middle and posterior lobes. *22.* Macroscopical photograph of the pancreas of a normal rat. *23.* Macroscopical photograph of the pancreas in the alarm reaction (elicited by 5 days' treatment with atropine). Note the distinctly visible white Langerhans' islets along the blood vessels. Pancreatic lobules are atrophic and translucent. *24.* Section through a pancreas in the alarm reaction (elicited by excessive muscular exercise). Secretory granules (extremely eosinophilic) are seen in the neighborhood of the islets; the remaining acinar tissue shows no sign of secretion.

organs 48 hours after the first injection is given in table 1. The weights given in this and following tables represent averages from the entire group. The numbers in brackets represent the smallest and the largest weight noted. Six rats, 3 months of age, have been used in each group. The weight of the iliac group of lymph glands has been recorded as a representative sample of the

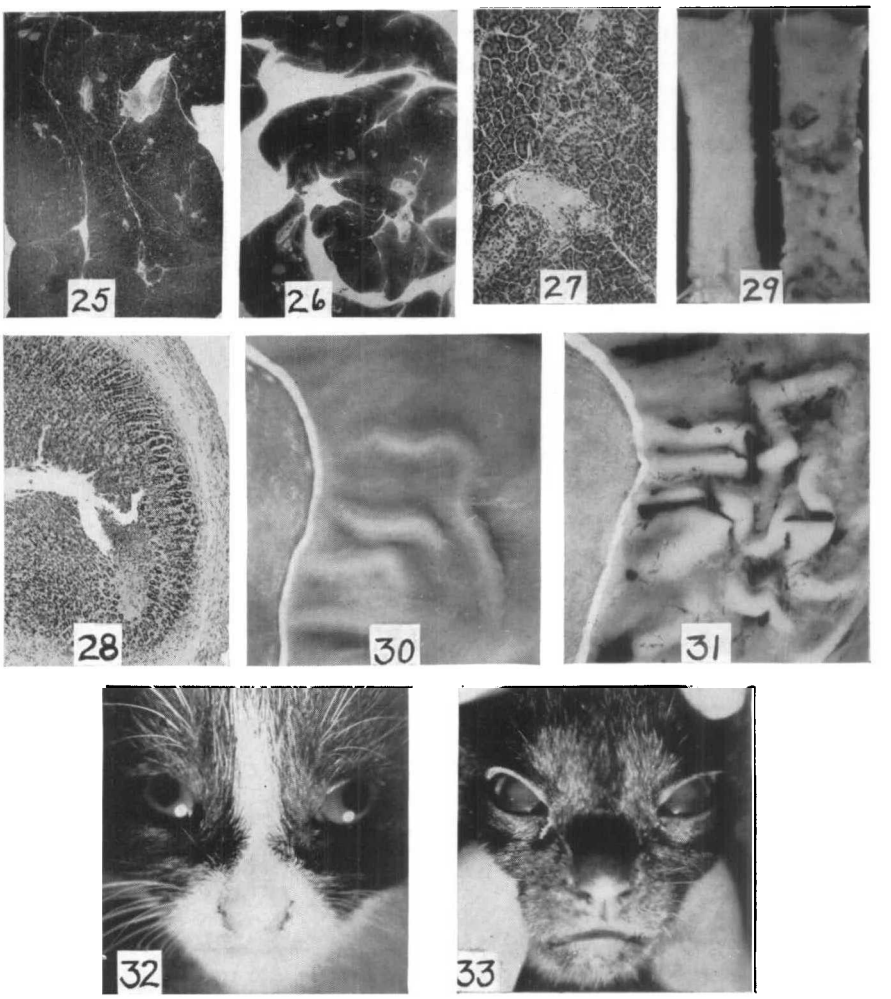

Fig. 25-33. *25.* Low magnification of pancreas of a normal rat. *26.* Pancreas in the alarm reaction (elicited by intoxication with formaldehyde), at same magnification as *25.* The Langerhans' islets are greatly enlarged and very numerous. *27.* Section of the pancreas in the alarm reaction (elicited by exposure to cold), showing cells which seem to represent intermediate stages between acinar and islet cells. *28.* Ulcer covered by a slough of necrotic material in the depth of a fold in the gastric mucosa of a rat in the alarm reaction (elicited by formaldehyde intoxication). *29.* Macroscopical photographs of the mucosa of the small intestine; left, normal mucosa; right, mucosa covered with deep ulcers in the alarm reaction (elicited by exposure to cold). *30.* Macroscopical photograph of the gastric mucosa of a normal rat; left, the proventriculus; right, the secretory epithelium of the ventriculus. *31.* Deep hemorrhagic ulcers in the gastric mucosa in the alarm reaction (elicited by exposure to cold). *32.* Eyes of a normal cat. *33.* Cataract formation in the cat in the alarm reaction (elicited by exposure to cold).

lymphatic system. This group consists of 4 nodes, 1 on each side of the inferior vena cava above its bifurcation into the 2 iliac veins, 1 just below the bifurcation between the 2 iliac veins, and 1 in the mesentery of the rectum just ventrally to the last-mentioned node.

From table 1 it is obvious that after 48 hours—that is, at the end of the first, or alarm stage of the adaptation reaction—the most striking changes are the sudden involution of the thymus, and less regularly that of the lymph glands and spleen; furthermore, the marked hypertrophy of the adrenals. The histological changes in these organs will be described later, together with microscopical changes in other organs not accompanied by marked variations

in total weight. It will suffice here to discuss those most outstanding features of the alarm reaction which make the diagnosis of the syndrome possible, and thus allow one to discover the conditions which will elicit an alarm reaction. In addition to the changes in the weight of the lymphatic organs and the adrenals, a characteristic symptom is the formation of gastric and intestinal erosions which, although not constant, are frequently observed during the acute stage. They do represent an essential symptom, however, and are invariably observed if adrenalectomized animals are exposed to alarming stimuli. The effect of adrenalectomy on the development of these gastro-intestinal changes will be discussed later. The water retention and edema formation so characteristic during the first 24 hours of the alarm reaction subside at the end of this stage and are only rarely observed after 48 hours.

TABLE 1. CHANGES IN THE WEIGHT OF THE LYMPHATIC ORGANS AND THE ADRENALS IN THE ALARM REACTION. AVERAGE, SMALLEST AND LARGEST WEIGHTS, IN MG.

	Thymus	Lymph Glands	Spleen	Adrenals
Untreated	*258*, (172, 400)	*38*, (19, 72)	*850*, (440, 1,400)	*53*, (44, 62)
Adrenaline	*94*, (70, 114)	*26*, (22, 34)	*520*, (300, 800)	*63*, (56, 80)
Formaldehyde	*85*, (72, 110)	*15*, (10, 29)	*370*, (200, 540)	*67*, (54, 75)
Morphine	*114*, (97, 195)	*36*, (26, 46)	*740*, (370, 900)	*67*, (62, 78)
Atropine	*124*, (72, 285)	*32*, (19, 38)	*810*, (750, 870)	*80*, (60, 100)
Spinal Shock	*114*, (64, 230)[1]	*18*, (12, 24)	*560*, (520, 630)	*63*, (58, 68)
Surgical Shock	*88*, (51, 170)	*26*, (18, 34)	*570*, (510, 640)	*61*, (40, 70)
Cold	*137*, (81, 187)	*24*, (18, 27)	*540*, (240, 700)	*62*, (54, 80)
Exercise	*124*, (77, 215)	*34*, (23, 62)	*620*, (380, 900)	*62*, (48, 74)

[1] Since the thymus edema had not quite subsided within 48 hours in this group the weights do not give an accurate image of the amount of thymus tissue left at this time.

As mentioned above, not only drugs but many other damaging stimuli may evoke an alarm reaction; the following examples illustrate the production of this syndrome by surgical shock, spinal shock, exposure to cold, and excessive muscular exercise. In every one of these cases, groups of 10 female rats, 3 months of age, were used, 4 of which were killed during the first 8 to 24 hours, and showed symptoms identical with those seen after the administration of alarming doses of various drugs. The only noteworthy difference was the higher incidence of gastro-intestinal ulcers in the group in which the alarm reaction was elicited by means other than drugs. Surgical shock was produced under ether anesthesia by exposure of the intestines for a period of 1.5 minutes, during which time the alimentary tract, the spleen, and omentum were exteriorized and slightly handled. Spinal shock was elicited by transverse section of the spinal cord just below the level of the vertebra prominens. The group exposed to cold was placed in an icebox at a temperature of —6°C. during the entire period of the experiment, 48 hours. The animals in which the effect of excessive muscular exercise was studied were placed in revolving cages having a diameter of 12 inches, which were driven by an electric motor at a speed of 18 to 22 revolutions per minute, for 1.5 hours twice daily. The weight changes observed in the lymphatic system and in the adrenals after 48 hours are summarized in table 1.

From this it is obvious that the changes caused by these various procedures are identical with those observed after the administration of alarming doses

of various drugs. The increase in adrenal weight and decrease in thymus weight are especially characteristic and constant. The atrophy of the lymph glands and the spleen, though always detectable by microscopical investigation, is not so apparent when judged by the gross weight.

It is concluded that the alarm reaction really represents a response to damage as such and not to any specific action of the drugs or other damaging agents tested. One would be tempted to interpret the well-known fact that extensive skin burns often cause gastro-intestinal erosions and concomitant adrenal changes in humans as an expression of the alarm reaction. In this connection it is of interest to mention the work of Horton, Brown and Roth (6), who found in the course of observations on human subjects, that immersion of the extremities in cold water will increase gastric secretion, decrease the blood pressure and cause marked generalized hyperemia of the skin, particularly in certain predisposed individuals. They interpret this response as being due to histamine liberation. In connection with our work on the effect of excessive muscular exercise, the observations of Andersen (7) are of interest. This author found slight decrease in thymus size without histological changes, and an increase in the lipoid content of the adrenals, in rats after exercise. The reason for her failure to observe the histological characteristics of accidental thymus involution and the loss of cortical lipoids here described, is possibly that the autopsies were not performed at the same stage of the reaction, and that the exercise used in her experiments was perhaps not as exhausting as under the conditions of our experiments. Recently, Anrep and Barsoum (8) demonstrated an increase in the histamine content of the venous blood coming from muscles during contraction. This finding seems to be in accord with the theory attributing the symptoms of the alarm reaction following excessive muscular exercise to an over-production of H-substance. In connection with the condition of spinal shock, the experiments of Ungar and his coworkers (9, 10) are of the greatest interest. They show that excitation of the peripheral stump of the purely sensory internal saphenus nerve increases the gastric secretion in the dog. This effect is not obtained if the femoral vein is ligated. The effect is not abolished by atropine. This fact, and the shape of the secretion curve indicate, according to the authors, that the active principle is probably histamine-like in nature. This would imply that H-substance is formed in peripheral tissues under the influence of nervous stimuli, and it is possible that a similar mechanism is at work in the production of the symptoms of the alarm reaction in the condition of spinal shock described above. Tinel and Ungar (11) showed, furthermore, that injection of zinc chloride and silver nitrate solutions into an artery of the dog's paw causes a sharp rise in the gastric secretion which is more marked immediately after transcision of the crural and ischiadic nerves than if the innervation of the paw is intact. It is not seen, however, after the nerves have undergone complete degeneration. This has been ascribed to the liberation of histamine-like substances from the tissues of the paw under the influence of these drugs.

This section on alarming stimuli should not be concluded without mention of the fact that parenteral administration of substances which are removed from the site of injection by phagocytosis rather than by simple absorption (such as rat blood, cholesterol emulsions, kerasin emulsions, egg-yolk and egg-white) cause an increase in the size of the lymph glands, the spleen and the liver. In this, the response to high doses of these substances differs from the usual type of the alarm reaction, even though thymus involution and adrenal hypertrophy are present just as after other alarming stimuli.

While all the substances of this series enlarged the lymph glands, the

spleen and the liver, the group treated with egg-white showed rather singular symptoms and therefore deserve a more detailed description. Twelve female rats, 3 months old, received an intraperitoneal injection of 1 cc. of pure, fresh egg-white. One to 3 hours following the injection, all of them showed marked subcutaneous edema with a characteristic distribution. The face, tongue, paws and clitoris were greatly swollen and edematous; the color of the edematous regions was bright red because of the accompanying hyperemia (see fig. 1, 2 and 3). A similar, but less pronounced edema was elicited by a second injection of 1 cc. the next day, while on the third day 6 of the animals, and on the fourth day all of them, failed to react. It appears that habituation occurred to this particular effect of the egg-white. In another experiment it was shown that this peculiar effect of egg-white (which was never observed after any other substance) may also be inhibited by giving a single injection of an alarming drug just prior to the injection of the egg-white. A group of 12 female rats, 3 months old, received 0.25 cc. of a 4 per cent formaldehyde solution subcutaneously, and immediately after this 1 cc. of egg-white intraperitoneally. Only 2 of them showed any subcutaneous edema, and even in these the reaction was delayed and very mild. That this inhibition is not simply the result of the lowered vitality of these animals was shown in a third group of 12 female rats, 3 months old, which received an injection of 1 cc. of egg-white intraperitoneally 24 hours after adrenalectomy. They all developed very marked subcutaneous edema which differed from that seen in normals only in that it was accompanied by cyanosis and not by arterial hyperemia. These animals were so severely damaged by this injection that all but 3 died within 48 hours. The significance of this peculiar reaction to egg-white is not clear, but it seems evident that in this case an alarm reaction, elicited by another drug, exerted a protective influence. As a rule the adaptation is specific, however, and numerous experiments have shown that while adaptation is acquired to a certain stimulus the animals become less resistant to other stimuli.

SYMPTOMS OF THE ALARM REACTION

One of the most striking and constant changes is the involution of the *lymphatic organs*. The loss of weight is most marked and rapid in the thymus (fig. 4 and 5). Here the characteristic cells of the parenchyma, the thymocytes, actually disintegrate and 24 hours after the onset of a severe alarm reaction only the debris of their chromatin is left (fig. 6 and 7), lying partly free in the reticulum, partly in phagocytes which are engaged in removing it. At this stage, the connective tissue stroma of the organ is usually very edematous, so much so that the entire organ assumes a gelatinous appearance which makes the naked-eye diagnosis of the condition easy. The cells of the reticulum, on the other hand, show signs of hyperplasia and by the end of 48 hours many of them assumed an epithelial appearance. They become round, their cytoplasm becomes more voluminous, and they form irregular strands of polygonal cells, tubules and even cysts, which are filled with an eosinophilic colloid similar to that seen in thyroid acini. Transitions between these new formations and typical Hassall bodies are frequently seen, and a close relationship between the two is obvious (see fig. 8, 9 and 10). The epithelial structures just de-

scribed may represent undifferentiated and hyperplastic precursors of Hassall's corpuscles. The extremely basophilic nuclear debris is usually removed by the end of 48 hours, and then only the now modified reticulum is left. This explains the great loss in total weight which the organ exhibits at this time. The lymph glands also show signs of involution, but without any noticeable hyperplasia of the reticulum. The involution in them usually begins in the germ centers, which may disappear almost completely (fig. 11 and 12). Nuclear debris is seldom found in the lymph glands and never abundantly as in the thymus, possibly because many of the lymphocytes emigrate from the lymph glands without previously undergoing necrosis, or because the drainage is better in the lymph glands than it is in the thymus, so that the debris is removed more rapidly and consequently never accumulates to any great extent in the organ. Frequently the sinuses of the lymph glands are filled with erythrocytes, so that the glands assume the appearance of hemolymph nodes. The spleen and the bone marrow usually contain but little of the nuclear debris and edema which are so characteristic of the thymus in this reaction. The atrophy of the spleen begins in the center of the Malpighian follicles and the white pulp is more severely affected than the red (fig. 13 and 14).

The *adrenal cortex* shows signs of marked hyperplasia in the alarm reaction. During the first 24 hours this is associated with a rapid loss of its lipoid granules. This loss of lipoids is apparent upon gross inspection, since the organ loses its characteristic light-yellow color and turns dark brown. In fact, this large brown adrenal, usually embedded in a translucent layer of retroperitoneal edema is probably the most typical macroscopical sign of an alarm reaction. Microscopic examination of frozen sections stained with Sudan III show that practically all Sudan-tingible granules have disappeared at this time. At the end of the alarm stage, the lipoid granules reappear, first in the shape of extremely fine, powder-like dots, more evenly distributed throughout the various layers of the cortex. Later they enlarge and localize more particularly in the zona fasciculata; that is, in that layer which contains most of these granules in normal, untreated animals. This reappearance of the lipoid granules at the end of the alarm stage was observed even if exposure to the alarming stimulus was continued, and the cortex was usually found to be loaded with lipoids during the second or resistant stage of the adaptation syndrome, irrespective of the nature of the stimulus to which adaptation occurred.

The *adrenal medulla* loses its chromaffin granules during the stage of alarm. Vacuoles appear in the periphery of its cells, and if the alarm reaction is very severe the cells may even undergo necrosis (fig. 15 and 16). In several cases this necrosis was so widespread that normal, live endocrine, or nerve cells could not be detected in the medulla of either adrenal. The stroma of the medulla and that of the adrenal cortex, however, were not markedly damaged. One cannot say, of course, whether these particular animals would have survived, and whether regeneration of the medulla would be possible in such severe cases, but animals in the resistant stage show no such signs of medullary damage, and even the chromaffin granules reappear after a certain

time. The paraganglia have not as yet been examined, but if a similar necrosis should also take place in the extra-adrenal accumulations of chromaffin tissue, such animals in the alarm reaction, or immediately after recovering from it, might prove of some use for the study of the symptoms of adrenaline deficiency. It should be mentioned in this connection that, apart from the extreme muscular weakness, the general condition of the animals in which the necrosis of the medulla was complete did not differ appreciably at the time they were killed from that of other rats in the same group which recovered.

The *hypophysis* also shows very characteristic changes in all 3 lobes. In the anterior lobe very numerous pyknoses are invariably found during the acute stage. These pyknoses appear in patches in certain regions of the gland, while other parts remain relatively free (see fig. 17). After more chronic treatment with non-specific damaging agents, an increase in the number of basophiles is frequently observed, and many of these basophiles assume the 'signet-ring cell' appearance. They are not unlike castration cells (see fig. 18). The changes in the middle lobe are most obvious during the stage of alarm. They consist in degeneration of the epithelial cells, especially along the junction line between the middle and the posterior lobe (fig. 19, 20 and 21). The debris of such degenerated middle lobe cells invades the posterior lobe. Many degenerated and even relatively unchanged middle lobe cells are found at this time in the tissue of the posterior lobe. The changes in this part of the gland consist mainly of vacuolization of the posterior lobe tissue and infiltration with more or less degenerated debris of middle lobe cells. The vacuolization is most marked in the vicinity of blood vessels and is probably due to edema. In some places the degeneration of the middle lobe parenchyma goes so far that a cleft is formed in this lobe, so that the anterior lobe cells come in direct contact with the posterior lobe. A study of sections through such places may give the impression that anterior lobe cells might invade the posterior lobe through these channels directly. It is, however, difficult to decide whether this actually occurs or not. Some of the cells in the posterior lobe are filled out with vacuoles so that their cytoplasm assumes a foam-like appearance. These cells of the posterior lobe correspond to the 'Schaumzellen' of the German authors. They are normally present in the posterior lobe of senile animals. It should be pointed out that the signet-ring cells are also physiologically present in the pituitary of senile (especially male) rats.

Very marked changes in the *pancreas* are revealed even on macroscopical inspection. The organ loses its natural whitish color, becomes pink and translucent. The Langerhans' islands are readily distinguishable in the form of white spots, usually situated along the course of the larger blood vessels (see fig. 22 and 23). Histological sections show that the acinar tissue has ceased to secrete in large areas of the glands; its cells are depleted of their secretory granules. They become round and very similar to the cells of the islands of Langerhans. In the immediate vicinity of the Langerhans' islands the acinar cells retain their secretory granules much longer than in regions farther away from them (fig. 24). The granules here are very eosinophilic and a halo of eosinophilic cells surrounding the Langerhans' islands is one of the characteristic physiological changes in the pancreas during the alarm reaction.

The Langerhans' islands themselves are usually enlarged, especially in the later stages, and many new islands are formed (fig. 25 and 26). These new islands seem to bud out from pancreatic ducts. Sometimes, however, one gains the impression that acinar cells undergo a direct transformation into island cells. One may find all intermediate stages between the typical acinar cell which rounds off after having lost its secretion granules and the characteristic Langerhans' islands cells. The question whether such direct transformation of acinar cells into endocrine cells is possible has not been decided as yet; while Opie (12) states that island cells may only be formed from ducts, but never from acini, Herxheimer (13) maintains that transitions are possible, and that island cells may be formed from acini and vice versa. Sections such as that represented in figure 27 certainly give the impression that islands do form from acinar tissue. However this may be, the fact remains that the enlargement of the Langerhans' island is not the result of any mitotic division of the island cells themselves, since in all our material we have seen only 2 cases of Langerhans' cells actually in the process of mitosis. The fact that the islands become so readily visible to the naked eye during the alarm reaction cannot be ascribed solely to their enlargement, however, but is due first of all to the fact that the acinar tissue assumes a translucent pinkish color after the secretory granules are lost, and thus the white islands become much more obvious.

The *gastric and intestinal ulcers* appeared histologically to be due to complete dissolution of the mucosa and are often accompanied by inflammatory infiltrations in the submucosa and muscularis (fig. 28, 29, 30 and 31). Perforating gastric ulcers have repeatedly been observed; they led to abscess formation in the peritoneal cavity in the immediate vicinity of the perforation. Generalized peritonitis never ensued, since adhesions of the omentum and intestines demarcated the inflammatory process.

It is hardly within the scope of this communication to discuss fully the literature concerning the production of gastric ulcers by various experimental procedures. We feel, however, that it would be of some value at this time to correlate our findings with some of the more significant observations which other investigators have made in this field. It will be recalled that such ulcers have been produced by a great variety of drugs, injuries to the vegetative centers in the hypothalamic region, skin burns, etc. A publication by Sun (14) is of particular interest in connection with the present observations. This author, studying the effect of starvation, found that the tips of intestinal villi disintegrate after 24 hours' starvation in the rat if the animals are kept at a surrounding temperature of 10°C., while in warmer surroundings longer starvation is necessary to produce the same result. The interesting observations made by Dodds and Noble (15) that extracts of the posterior lobe of the pituitary produce ulcers in the gastric mucosa of various animals may also have some relation to this problem. It is difficult to understand why such a variety of stimuli should act in an identical fashion. The theory that H-substance is liberated from the various tissues during the alarm reaction may give a plausible explanation of these observations. It is indeed well known that histamine causes marked erosions of the gastric mucosa in various animals (16, 17, 18, 19, 20, 21). These erosions are especially easily produced after adrenalectomy (2), while adrenalectomy in itself does not cause gastric erosions in the rat.

In connection with the production of gastric ulcers by hypothalamic in-

jury, it may be recalled that the experiments described earlier in this paper showed that transcision of the spinal cord also produces acute gastric and intestinal erosions. It seems that at least in the rat the lesion does not necessarily have to be in the hypothalamus, but that a condition of spinal shock exerts a similar effect. This does not mean, however, that an injury to the hypothalamic centers is not more likely to cause gastro-intestinal erosions than a lesion in any other part of the central nervous system, but it is very likely that erosions produced by hypothalamic injuries are only one of the symptoms of an alarm reaction caused by interference with the important centers of this region.

The effect of extracts of the posterior lobe of the hypophysis deserves special consideration. It would not be justifiable to consider the ulcers produced by vasopressin simply as a result of the nonspecific damage caused by high doses of this drug. Indeed, we found that the dose of vasopressin necessary to produce a gastric erosion is relatively small in proportion to its general toxic action. In this respect the effect of vasopressin, histamine, section of the spinal cord, excessive muscular exercise and exposure to cold differs from that of numerous drugs in that the former group invariably produce marked gastric erosions in the normal rat. In the case of drugs other than histamine or vasopressin, even lethal doses have little effect, if any, on the gastric mucosa of the normal animal, while marked erosions are produced by any one of them after adrenalectomy. These apparent discrepancies may be explained by the assumption that the specific toxicological action of the drug causes death before the organism was able to liberate enough H-substance to produce gastric erosions. In the case of exposure to cold, excessive muscular exercise or spinal shock, a form of intoxication with histamine-like metabolites is produced, uncomplicated by the toxicological effects of any exogenous pharmacological agent. Summarizing, it seems that the most plausible explanation of the gastric ulcers experimentally produced by various agents is the following. Various drugs and other damaging agents liberate H-substance from the tissues, which exerts a toxic effect on the mucosa of the stomach and intestines. This H-substance is detoxified by the adrenal or produced in unusually large quantities in the absence of this gland, so that ulcers are more readily obtained after adrenalectomy.

The *liver* also undergoes a marked loss of weight during the alarm reaction and occasionally shows fatty degeneration (demonstrated by staining frozen sections with Sudan III) or cloudy swelling. In rare instances focal necroses may form.

Cloudy swelling in the *kidneys* has also been observed. The urine is often stained with blood during the alarm reaction. Bladder hemorrhages have also been seen, but only in very severe cases.

Clouding of the *crystalline lens* was found only in especially severe cases. The clouding is transitory in nature and disappears if the animals recover from the alarm reaction. It has been observed in rats treated with various drugs or exposed to cold, and it was particularly common in a group of animals in which an alarm reaction had been elicited by tying their legs together for 48 hours, which led to excessive struggling during this period. The same

acute development of cataracts has been observed in 4 cats, 4 weeks of age, 3 hours after having been placed into a surrounding temperature of —1°C. As soon as they were warmed up again, the clouding disappeared. It is noteworthy that the formation of cataracts and of gastro-intestinal ulcers is especially common if the body temperature falls markedly below normal during the alarm reaction (see fig. 31 and 32).

STIMULI INFLUENCING THE COURSE OF THE ADAPTATION REACTION

The course of the adaptation reaction is very readily influenced by the conditions of the surroundings and even by the past history of the animals—that is, by those stimuli to which they have had to adapt themselves previously. One may even go so far as to say that it is not so much the dose in which a stimulus is given that makes it alarming as the condition of the animals at the moment when the stimulus is applied.

Hunger and cold are very active factors in aggravating the effects of alarming stimuli. In fact, cold or any other stimulus which is able to cause an alarm reaction by itself acts in a similar way. Thus it is possible, for instance, to obtain a typical alarm reaction by giving one quarter of the alarming dose of 4 different drugs within 48 hours, although one quarter of the alarming dose of any one of these drugs has no effect by itself.

The age and sex of the animals is also of importance. Old animals react more readily than young ones, possibly because much of their adaptation energy has already been used to meet the incidental demands of life. This probably explains also why resistance against almost any alarming stimulus is more difficult to obtain in fully adult rats, a fact which led to the use of animals 2 to 3 months of age in preference to older ones for the purposes of the present experimental series. Females show a more marked involution of the lymphatic organs after exposure to alarming stimuli than males. This may find its explanation in the fact that the adrenals are larger in the female rat than they are in the male.

The fact that hypophysectomy lessens the accidental involution of the thymus, and that adrenalectomy inhibits it completely, has been reported in a previous communication (22). So far, the only substances with which we have been able to cause thymus involution in the adrenalectomized rat are cortical extract and estrone (23). While adrenalectomy and, to a lesser extent, hypophysectomy, inhibit thymus involution, both of these operations facilitate the production of the other symptoms of the alarm reaction, such as the gastro-intestinal ulcers, the edema, the decrease in body temperature, and so forth. That hypophysectomy likewise inhibits the enlargement of the adrenal under the influence of alarming stimuli has also been noted (24).

Our recent experiments show that the lymph glands and the spleen, like the thymus, decrease in weight during the alarm reaction in the normal animal but not in the adrenalectomized rat. Table 2 summarizes a series of experiments which were performed on 3 months-old rats, using 10 males and 10 females in each group. Adrenalectomy was performed 48 hours before the first injection, and 4 injections of 0.5 cc. of 4 per cent formaldehyde were given subcutaneously within 2 days. All the adrenalectomized animals in this

TABLE 2. EFFECT OF THYROIDECTOMY, ADRENALECTOMY AND GONADECTOMY ON THE ORGAN WEIGHTS IN THE ALARM REACTION. AVERAGE, SMALLEST AND LARGEST WEIGHTS, IN MG.

Conditions of Experiments	Thymus	Iliac Lymph Glands	Spleen	Adrenals	Thyroid	Hypophysis
Normal untreated ♀s	*189* (135, 235)	*25* (14, 34)	*830* (760, 1000)	*59* (48, 69)	*19* (13, 24)	*8* (7, 10)
Normal untreated ♂s	*296* (262, 368)	*42* (26, 76)	*1000* (880, 1200)	*37* (31, 41)	*22* (18, 26)	*8* (6, 10)
Normal+formaldehyde. ♀s	*118* (61, 182)	*21* (10, 32)	*560* (260, 800)	*72* (60, 90)	*18* (16, 21)	*9* (8, 10)
Normal+formaldehyde. ♂s	*123* (74, 192)	*27* (18, 42)	*650* (470, 840)	*52* (42, 66)	*20* (18, 26)	*9* (6, 10)
Thyroidectomized ♀s	*185* (112, 250)	*22* (14, 35)	*730* (480, 850)	*49* (38, 61)		*10* (8, 12)
Thyroidectomized ♂s	*209* (166, 254)	*36* (20, 56)	*780* (450, 980)	*35* (30, 40)		*9* (7, 11)
Thyroidectomized+formaldehyde. ♀s	*104* (26, 160)	*13* (8, 22)	*240* (180, 370)	*56* (50, 60)		*9* (8, 11)
Thyroidectomized+formaldehyde. ♂s	*82* (42, 107)	*21* (14, 34)	*370* (200, 600)	*47* (36, 58)		*8* (7, 10)
Adrenalectomized ♀s	*276* (158, 345)	*36* (25, 53)	*800* (640, 850)		*18* (13, 20)	*10* (7, 12)
Adrenalectomized ♂s	*293* (182, 408)	*49* (33, 58)	*1600* (810, 1500)		*20* (14, 28)	*9* (7, 10)
Adrenalectomized+formaldehyde. ♀s	*238* (147, 320)	*46* (36, 60)	*770* (700, 840)		*16* (14, 20)	*10* (8, 11)
Adrenalectomized+formaldehyde. ♂s	*322* (230, 420)	*57* (39, 89)	*1800* (900, 1500)		*18* (9, 28)	*9* (7, 10)
Adrenalectomized and thyroidectomized. ♀s	*244* (167, 340)	*35* (27, 42)	*670* (500, 1000)			*8* (7, 9)
Adr. and thyr.+formaldehyde. ♀s	*210* (165, 250)	*17* (7, 25)	*770* (500, 1300)			
Spayed females	*375* (318, 415)	*39* (31, 53)	*1100* (820, 1300)	*50* (37, 71)	*19* (14, 22)	*13* (12, 16)
Spayed females+formaldehyde	*137* (75, 290)	*36* (20, 45)	*620* (340, 800)	*60* (51, 68)	*17* (16, 18)	*13* (10, 14)
Spayed males	*412* (263, 655)	*48* (35, 72)	*1220* (800, 1700)	*48* (42, 60)	*21* (15, 28)	*15* (12, 16)
Spayed males+formaldehyde	*193* (124, 250)	*33* (22, 48)	*740* (610, 820)	*52* (48, 60)	*18* (13, 20)	*13* (11, 14)

and the following experiments received a 0.9 per cent sodium chloride solution in place of drinking water, since such treatment with salt has been found to restore the resistance of adrenal-deficient rats to various drugs without restoring the ability of thymus to undergo accidental involution (22). The figures in the table represent the averages and (in brackets) the extreme variations of the organ weights 48 hours after the first injection.

In the same table are reported the organ weights of 20 male and 20 female rats, 3 months of age, which had been thyroidectomized 2 weeks before the first injection. Ten in each group were treated with formaldehyde and 10 left as untreated controls. This experiment was performed mainly because several authors claim to have obtained thymus involution after thyroidectomy. Thus Marine and his coworkers (25), studying the effect of adrenalectomy and thyroidectomy on the thymus of the rabbit, state that thyroidectomy causes thymus involution and prevents the hyperplasia of the

thymus otherwise observed after adrenalectomy. Hence they conclude that thyroid hormone is necessary for the thymus hyperplasia which usually follows adrenalectomy.

The figures in table 2 show no significant deviation from the normal in the thymus weight of thyroidectomized but otherwise untreated rats. It appears, therefore, that thyroidectomy as such does not cause thymus involution. The thyroidectomized animals treated with formaldehyde show, however, that a dose of this drug which is not fatal for normal animals killed 4 of 10 males and 8 of 10 females in the thyroidectomized group, with very severe symptoms of the alarm reaction. Gastric and intestinal ulcers were present in all but 2 animals in this series and the involution of the lymphatic organs was much more severe than it was in the normals. It appears that thyroidectomy, although it does not lead to an alarm reaction by itself, sensitizes the organism to alarming stimuli. This would also explain the observation that rats killed 2 to 4 days after thyroidectomy almost invariably have a small thymus, probably as a result of the accompanying surgical trauma. Within 14 days, however, the thymus reassumes its normal size. The completeness of the thyroidectomy was carefully checked at autopsy in every animal of this series.

Since these experiments show that adrenalectomy inhibits and thyroidectomy facilitates the involution of the thymus under the influence of alarming stimuli, it seemed of interest to establish how the lymphatic system of animals both adrenalectomized and thyroidectomized would respond. Twenty female rats, 3 months old, were adrenalectomized and 2 days later thyroidectomized. Then, after 9 more days, 10 of these rats were treated with formaldehyde in the same way as the other animals of this series. The remaining 10 rats served as controls. The organ weights of these animals, which are also included in table 2, show no significant deviation from the normal either in the formaldehyde-treated or in the non-treated group. From this we may conclude that thyroidectomy does not influence the inhibiting action which adrenalectomy exerts on the involution of the lymphatic organs following alarming stimuli.

It seems of interest, furthermore, to establish whether castration would have any effect on the course of the alarm reaction, since the ovarian hormone estrone was found to act as an alarming stimulus and even to occupy a rather special position among the alarming stimuli inasmuch as it led to thymus involution in the absence of adrenal tissue (23).

Twenty male and 20 female rats were gonadectomized at the age of 1 month—that is, 2 months before the time at which they were to be used for the present experiment. This lapse of 2 months between the operation and the experiment was allowed in order to permit the lymphatic system to show such changes as would occur after castration. At the age of 3 months these animals were divided into 2 groups. Ten male castrates and 10 female castrates were treated with an alarming dose of formaldehyde, while the remaining 10 animals of each group served as untreated controls. The results, which are summarized in table 2 show, first of all, that the great increase in body weight seen in older animals after gonadectomy was not noticeable in these young rats; in fact, their average weight was slightly below that of normal controls. The untreated, gonadectomized animals showed a great increase in weight, not only of the thymus but of all lymphatic organs. That

this increase was even more marked than that seen in the adrenalectomized group is not significant, however, since the adrenalectomies had been performed only 4 days before the animals were sacrificed, so that the lymphatic organs did not have as much time to proliferate as they had in the gonadectomized series. The sex difference in the size of the adrenals disappeared almost completely, for the adrenal weights of the male castrates were above and those of the female castrates slightly below normal. After treatment with formaldehyde, the characteristic involution of the lymphatic organs and hypertrophy of the adrenals was well marked, in both the male and the female castrates.

In connection with the apparent hypertrophy of the lymphatic organs following gonadectomy, it should be emphasized that these organs do not show true hyperplasia in the sense of an enlargement above normal size. They only tend to assume and maintain the maximum physiological size which they would have under optimum conditions at the optimum time of their development—that is, at about 2 months of age for the thymus, and 3 to 4 months of age for the lymph glands. Objection has already been made (22) to interpreting the condition of the thymus after adrenalectomy as a state of true hyperplasia. The thymus, the lymph glands and the spleen of a gonadectomized or adrenalectomized rat are never above the maximum size that these organs may assume in the normal under optimum conditions. It is true that the average size of the lymphatic organs of a whole group of adrenalectomized or gonadectomized animals will usually be above the average size of these organs in a group of normals, even at the age of their maximum development (2 to 3 months); but this is due only to the fact that the lymphatic organs of each individual animal in the gonadectomized and adrenalectomized group were in the vicinity of the upper limit of the normal. This seems of importance because it suggests that adrenalectomy affects the lymphatic organs merely by rendering inoperative such stimuli as would be liable to cause involution, rather than by direct stimulation of their growth, as has been previously assumed. The mechanism of action of gonadectomy is different, since removal of these glands, though it maintains the lymphatic organs in a condition of maximum development, is unable to prevent their involution following alarming stimuli. Since ovarian and testicular hormones are known to cause thymus involution, it seems likely that castration acts simply by removing the source of these hormones, which would exert a constant depressive action on the lymphatic organs of postpubertal animals.

In connection with the effect of adrenalectomy on the course of the adaptation reaction, one more point deserves mention. Although adrenalectomy decreases the resistance of the rat against alarming stimuli, such adaptations as have been acquired before adrenalectomy are not entirely lost after the removal of this gland. This is well shown by the following experiment performed on 60 female rats. Twenty of these animals were pretreated with subcutaneous injections of 1 per cent morphine sulphate solution in doses ascending from 1 to 3 cc. twice daily within one month. At the end of this period, these animals were 4 months old. At this time they were adrenalectomized, together with 20 non-pretreated controls of the same age. Beginning 24 hours after this operation, these 40 adrenalectomized animals and 20 non-pretreated normal controls of the same age received 3 cc. of the morphine

solution twice daily for 3 consecutive days. While all of the non-pretreated adrenalectomized animals died during this time, only 5 of the pretreated adrenalectomized, and only 2 of the non-pretreated normals succumbed. Since all of the pretreated animals tolerated this dose of morphine before the operation, while 2 of the non-pretreated normals receiving the same amount died, one may conclude that a certain adaptation to morphine has occurred by this time. This adaptation was decreased by removal of the adrenals, since 5 of the pretreated animals died following the operation. Still, one may conclude that this adaptation was not entirely lost after adrenalectomy, for 75 per cent of the pretreated adrenalectomized animals survived, while none survived in the adrenalectomized, non-pretreated group.

DISCUSSION

In 1913 the Belgian histologist Dustin studied the effect of certain drugs on mitotic divisions and nuclear pyknosis. More recently, he has summarized the results of his extremely interesting cytological observations (26). He states that a certain group of drugs which he terms 'poisons caryoclasiques' decreases the number of mitotic figures in the thymus and lymph glands of the mouth and increases the number of pyknoses. In a later stage, regeneration with increase in the number of mitoses occurs. He and his pupils found that definite mitotic waves may occur under the influence of these same drugs in other organs such as the liver, Langerhans' islands of the pancreas, the adrenals, the spleen and the intestinal epithelium. Cytological studies along these lines, after surgical and nervous injuries, after exposure to cold, and after the administration of sublethal doses of drugs other than the 'poisons caryoclasiques' would be necessary in order to establish the exact correlation between this apparently specific cytological reaction to certain drugs and the alarm reaction. Only if the same cytological changes could be elicited with non-specific stimuli, and on the other hand the 'poisons caryoclasiques' should produce other typical symptoms of the alarm reaction (water retention, gastro-intestinal ulcers, adrenal enlargement, drop of body temperature, etc.) and should lose their effect on the lymphatic system after adrenalectomy, would we feel justified, however, in doubting the specificity of the action of this group of substances.

In 1921 the French clinician Widal and his school gave a great deal of attention to the clinical syndrome which Widal termed 'crise hémoclasique.' This reaction was first observed by this author in cases of cold hemoglobinuria, and was later seen in numerous other clinical conditions such as acute infectious diseases, allergic conditions, etc.

The reaction has chiefly been studied from a hematological point of view. Its outstanding features are leucopenia, decrease in the refractive index of the serum, decrease in blood coagulation time, and decreased blood pressure; occasionally albuminuria and fever are also observed, and these latter are not constant symptoms. Since both Widal's reaction and the alarm reaction seem to represent responses of the organism when suddenly confronted with critical situations, a certain relationship between the two might be suspected.

The possible bearing of our observations on the theory of non-specific therapy, about which so little is known as yet, should also be mentioned.

Weichardt, in his recent monograph (27) gives an excellent review of the experimental and clinical observations made in this connection. He and Schmidt (28) developed the idea that non-specific therapy leads to the production of metabolites, which increase the efficiency of the organism and its individual organs ("Leistungssteigerung und Protoplasmaaktivierung"). It is quite likely that close correlations exist between alarming stimuli and non-specific agents.

The conception of tachyphylaxia and skeptophylaxia should also be mentioned in connection with our experiments on adaptation. In 1911 Champy and Gley (29) called attention to the fact that injection of small quantities of toxic organ extracts will protect animals against larger doses of the same extract administered shortly afterward. The name 'tachyphylaxia' has been given to this phenomenon, in order to emphasize both its possible relationship to anaphylaxia and the great rapidity with which the protective effect develops. The protection in the condition of tachyphylaxia is extremely transitory in nature and lasts for a few hours only. In the same year Ancel, Bouin and Lambert (30) described very similar results under the name of 'skeptophylaxia,' also emphasizing the transitory nature of the protection obtained by the first injection of the organ extract against subsequently administered toxic doses. It is possible that a certain relationship exists beween tachyphylaxia or skeptophylaxia and the conditions of adaptation described in this communication. Attention should be called, however, to the fact that these phylactic reactions last for a few hours only, while the adaptation which we obtained is more permanent, although we do not know as yet exactly how long it lasts.

The fact that in the course of the adaptation reaction the resistance acquired during the resistant stage gradually disappears again, so that exhaustion occurs, suggests that the animal runs out of something which is indispensable for adaptation. The other observation—that an animal which has had to adapt itself to a certain damaging stimulus while acquiring resistance to this one loses part of its ability to resist injuries of a different nature—also suggests that something is actually used up during every process of adaptation. Since nothing is known at the time about the nature of this adaptation principle, we shall simply refer to it as 'adaptation energy.'

SUMMARY

A reaction is described under the name of 'alarm reaction' which represents a non-specific response of the organism to damage as such. Its main symptoms are: adrenal enlargement, involution of the lymphatic organs, degeneration and death of cells in various tissues, ulcer formation in the digestive tract, and edema formation. These symptoms are the same whatever the specific nature of the damaging agent may be. Drugs, surgical injuries, spinal shock, excessive muscular exercise, all elicit this same reaction.

Experiments on rats show that, if the organism is exposed daily to a stimulus causing an alarm reaction in the beginning, it will eventually become adapted to this stimulus. This adaptation, however, is lost after some time, apparently because the organism runs out of something needed for the fight against the damaging agent. At this time the animals die in a condition of

exhaustion, with symptoms similar to those seen in the acute stage of alarm. The whole reaction of adaptation consists, therefore, of 3 stages: the stage of alarm, the stage of resistance, and the stage of exhaustion. Evidence is advanced which seems to support the hypothesis that the symptoms seen in the stage of alarm are due to the liberation of a histamine-like substance.

The histological changes occurring during the reaction of adaptation are described. Adrenalectomy prevents the involution of the lymphatic organs but facilitates the production of all the other symptoms of the alarm reaction. Thyroidectomy does not cause involution of the lymphatic organs by itself, but facilitates the production of all the symptoms of the alarm reaction, including the involution of the thymico-lymphatic apparatus following exposure to damaging agents. The thymico-lymphatic apparatus of gonadectomized male and female rats does not show true hyperplasia but it approximates the upper limit of the normal, and shows no involution with advancing age. Gonadectomy does not, however, prevent the accidental involution of the thymus and the lymph glands during the alarm reaction. While adaptation is acquired to a certain stimulus, the ability to resist other stimuli decreases. The adaptation in the stage of resistance is therefore specific. The hypothesis is put forward that the factor necessary for adaptation, 'the adaptation energy,' is present in every individual in a limited quantity only.

I am greatly indebted to Professors J. B. Collip and D. L. Thomson, and to Dr. J. S. L. Browne for their stimulating criticisms which proved to be of the greatest value in conducting this work. It is a pleasure, furthermore, to take this opportunity to express my gratitude to the technicians of the department, and particularly to Mr. K. Nielsen.

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