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INTRODUCTION

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The Adrenal Cortex as a Regulator in Tissue Reactions¹

By **R. Levine M.D.**

Herr Präsident,
Meine Damen und Herren,

Erlauben Sie mir, der Schweizerischen Akademie der Medizinischen Wissenschaften meinen herzlichen Dank auszusprechen für die mir bewiesene Ehre, mich am Symposium beteiligen und die Einführung zum Thema der Tagung halten zu dürfen. Das Referat lese ich in der englischen Sprache, deren Nuancen ich besser beherrsche als eine der vier Sprachen Ihrer Heimat.

In the summer of 1949 a group of patients with severe rheumatoid arthritis was studied in the Metabolic Unit of the Michael Reese Hospital, before, during and after cortisone and adrenocorticotrophic hormone (ACTH) therapy, with the hope that one of the metabolic or endocrine parameters would bear some regular and definite relation to the effect of these substances on the signs and symptoms of the disease. This hope was not fulfilled, but the study led to the formulation of the following general concepts. Cortisone affected symptoms and signs of inflammation without necessarily exerting any major effect on gross metabolic phenomena such as protein, carbohydrate, or mineral, transformations. Regardless of whether glucose tolerance, insulin sensitivity, and other metabolic functions, were or were not affected, the relief of signs and symptoms occurred in every case and usually preceded any major metabolic changes. When therapy was discontinued, the flare-up of signs and symptoms could not be correlated with the degree or direction of level, or with the excretion, of any of the substances measured. The fact that the inflammatory phenomena reappeared in the same locations in which they were lodged before therapy was started, appeared

¹ The work reported was aided by a grant from the U.S. Public Health Service to the Rheumatoid Arthritis Research Group of Michael Reese Hospital.

to us to indicate that cortisone acted locally on the affected tissue. This was corroborated later by the effect of cortisone on certain inflammatory conditions of the eye when a suspension of the drug was instilled locally. In experimental chemical abscesses, cortisone pretreatment inhibits fibroblastic proliferation, but the same effect can be obtained when a small amount of cortisone is mixed with the turpentine used to initiate the abscess—again, therefore, presumptive evidence for the local action of cortisone on inflammatory tissue (1–3).

An analogous situation existed, we thought, in the effect of adrenocortical extract (ACE) on the signs and symptoms of Addisonian crisis. The intravenous administration of aqueous ACE to a patient in crisis raises the blood pressure and relieves the extreme weakness and gastrointestinal symptoms long before there are any measurable changes in the electrolytes, non-protein nitrogen, or sugar of the blood. We therefore decided to approach the study of cortisone action by analyzing in detail the effects of this substance on stress and its sequellæ in the adrenalectomized animal. The type of stress employed initially was muscular exercise because of the convenience and partially quantitative nature of such a procedure. It is well known that adrenalectomized animals, in excellent clinical condition while being maintained on desoxycorticosterone acetate (DOCA), fatigue very rapidly when subjected to continuous muscular exertion such as swimming or electrical stimulation (4–5). Contractions diminish in force very rapidly, and then cease. Not only are the muscles affected, but the animal goes into «shock» and soon dies.

The easy fatigability of the adrenalectomized animal has been attributed to some «metabolic» disturbance in the muscle since the hormones that could repair this disturbance were the so-called glucocorticoids,

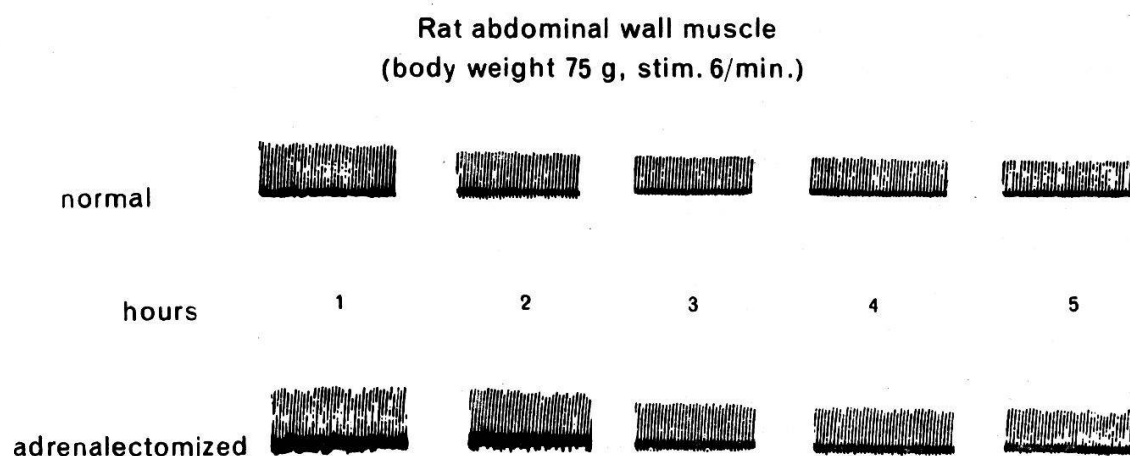


Fig. 1. Direct electrical stimulation of muscle in vitro. Note that there is no significant difference in the height of contraction between adrenalectomized and normal muscle even after 5 hours of work. (From Amer. J. Physiol. 162, 110 [1950].)

which are concerned in some way in foodstuff metabolism (5-7). This hypothesis was tested in the following way. Suitable thin muscle strips removed from normal and adrenalectomized rats were suspended in an oxygenated buffered medium. These muscles were then stimulated electrically to contract at a definite rate, and the contractions were registered on moving paper. Some muscles (diaphragm) were also stimulated through the attached motor nerve. The experiments demonstrated that the isolated muscle and the nerve-muscle preparation of the adrenalectomized animal were capable of the same amount of work as the normal muscle under the same experimental circumstances (8) (fig. 1 and 2). The fatigability exhibited *in vivo* cannot therefore be due to intrinsic disturbances in the nerve, the myoneural junction, or the muscle fiber.

It was a natural step to pursue this work further by postulating that *in vivo* a factor other than muscle function itself is involved. A muscle working *in vivo* requires a normally functioning neurocirculatory reflex network that can evoke the necessary increases in blood flow to the working part and can at the same time lead to a decrease in the splanchnic vascular bed in order to preserve normal hemodynamic conditions. The adrenalectomized animal may not be able to make these necessary neuro-circulatory adjustments over long periods of time. It might therefore be expected that under stress, vascular collapse would be the end result of improper circulatory adaptation. The fatigability of muscle would then be due to a fall in blood pressure and the consequent diminution in flow through the working part.

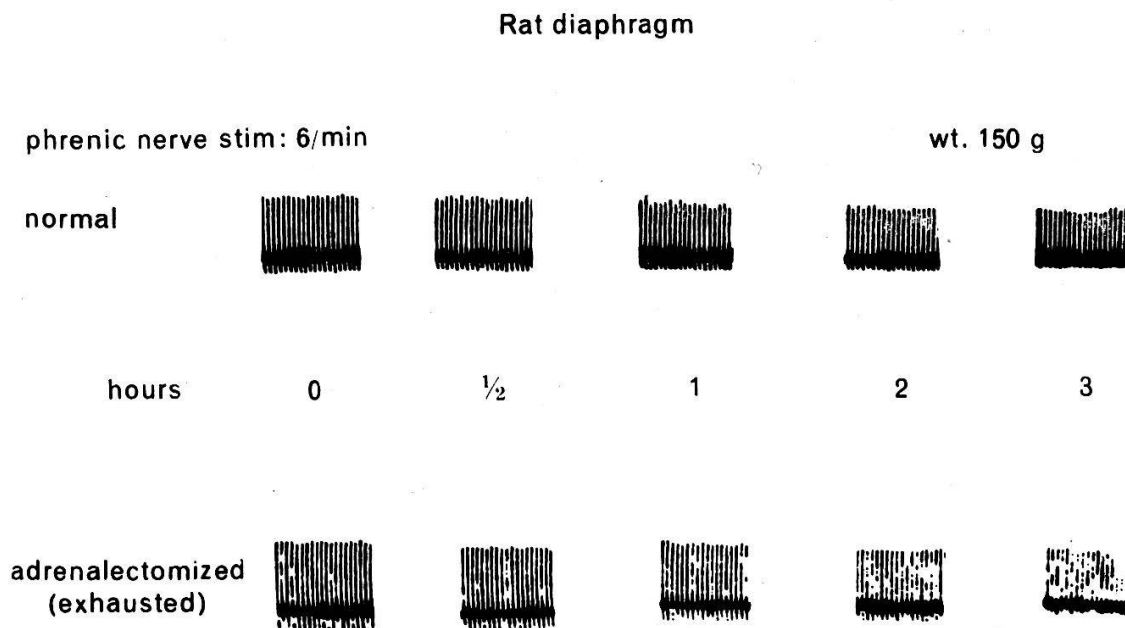


Fig. 2. Same as fig. 1 except that diaphragm was stimulated via its nerve supply.
(From Amer. J. Physiol. 162, 10 [1950].)

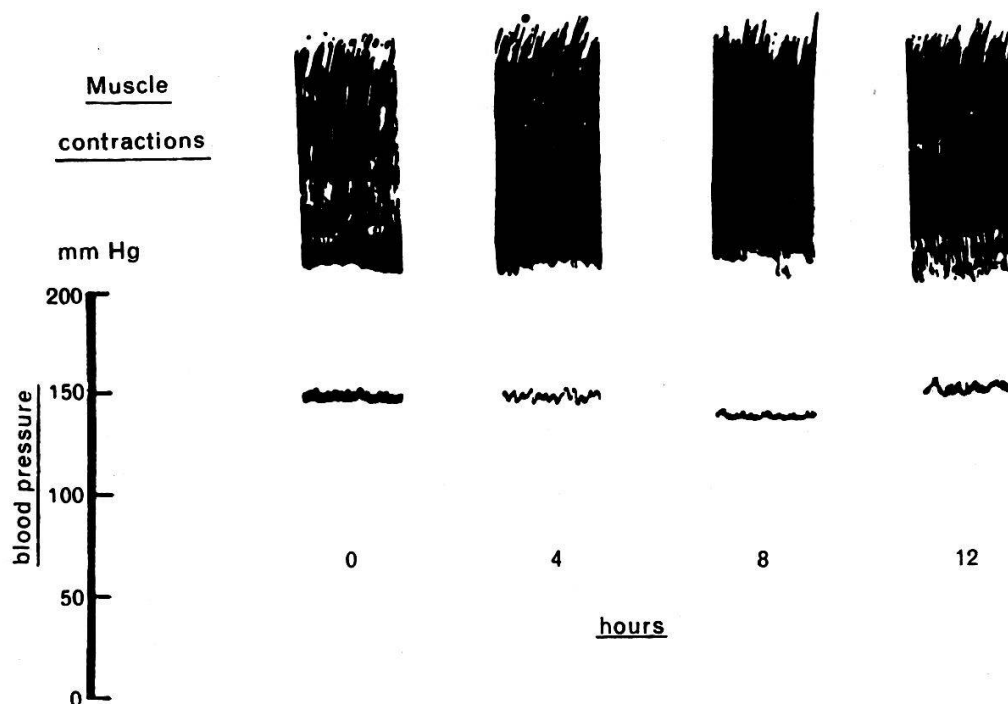


Fig. 3. Normal dog, weight 19 kg; right gastrocnemius muscle stimulated in situ at 3/sec.; 2-kg load. Note the excellent circulatory adaptation to uninterrupted stimulation of the muscle for 12 hours, as shown by maintenance of initial blood pressure level. No muscular fatigue under conditions shown.

This hypothesis was tested in the following manner: Normal and DOCA-treated adrenalectomized dogs were anesthetized and the gastrocnemius-soleus group of muscles was stimulated electrically. The muscles were contracting against a suitable weight suspended from the severed Achilles tendon. In the adrenalectomized animal, fatigue set in within one to three hours from the beginning of stimulation. In the normal control group, no fatigue was demonstrable even after twelve hours of continuous contraction. The femoral blood pressure was simultaneously recorded and the data obtained showed that significant falls in blood pressure occurred in the adrenalectomized animal considerably before the contraction record showed any degree of fatigue (fig. 3 and 4). The onset and degree of fatigue depended on the height of the blood pressure below a critical level of about 70 mm Hg. In the adrenalectomized group the blood pressure continued to fall even after fatigue set in, and all the animals died in «shock». The heart rate did not change significantly; neither did the venous pressure. It can be concluded, therefore, that 1. the muscular fatigue is secondary to, and a symptom of beginning, vascular incompetence, and 2. this vascular disturbance is in the main a dysfunction of the peripheral circulation rather than a result of cardiac failure (8, 9).

In experiments such as described, attempts were made to restore

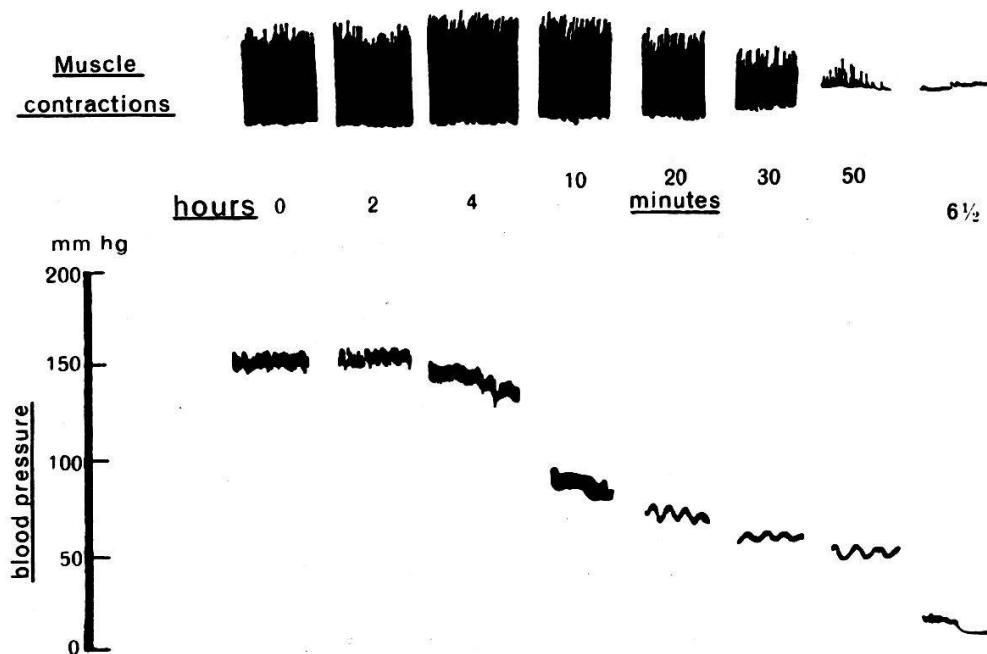


Fig. 4. Adrenalectomized dog, weight 7.6 kg; right gastrocnemius muscle stimulated in situ at 3/sec.; 1-kg load. Conditions of stimulation the same as shown in figure 1. Note that the adrenalectomized dog (despite adequate DOCA therapy) adapts poorly to demands of muscle work. Fall in blood pressure precedes muscular fatigue by an appreciable period. The animal dies as a result of circulatory failure induced by the attempt to adapt to stress. (From Amer. J. Physiol. 163, 561 [1950].)

normal blood pressure levels by means of infusions of blood and the administration of vasoconstrictor agents. The effects of these measures were always temporary, but they served to demonstrate that with the rise in blood pressure there was an immediate awakening of the dormant muscular activity to the prefatigue levels (10).

In order to gain insight into the mechanism of the inexorable peripheral vascular failure that followed muscle stimulation, it was decided to determine the behaviour of noradrenalin in the anesthetized-adrenalectomized animal under varying conditions. Noradrenalin was chosen because of recent experimental evidence that it is most probably the normal physiologic vasoconstrictor substance liberated at the nerve endings of the adrenergic system. The data showed that the adrenalectomized animal was less sensitive to the blood-pressure-raising effects of noradrenalin, whether the drug was given intermittently or by continuous infusion. The longer an animal had been under the stress of anesthesia, the more refractory it became to the vascular effects of this sympathomimetic substance (fig. 5, 6, 7). If, however, ACE (aqueous, Upjohn) was injected during the relatively ineffective infusion of noradrenalin, the blood pressure rose temporarily to high levels (fig. 8). DOC-glucoside did not have this effect. Neither did ACE in the absence of noradrenalin (10). The tentative conclusion reached at this point was that the adrenal-

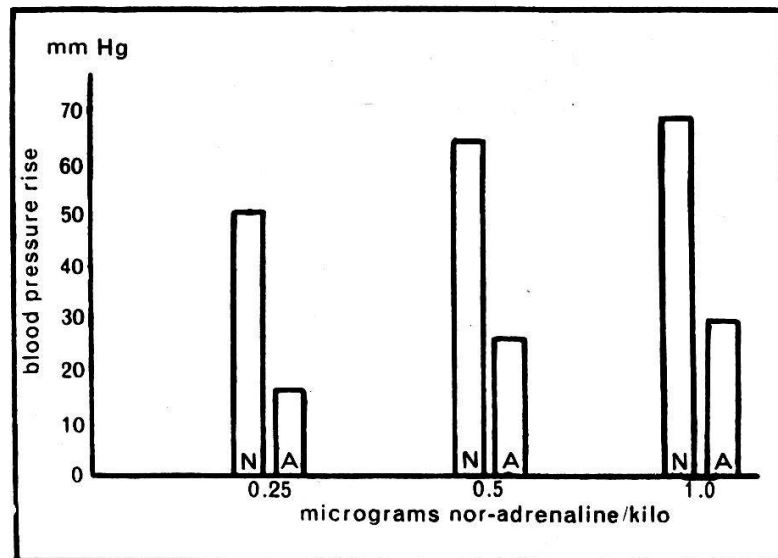


Fig. 5. Average blood pressure rise above base levels (in mm Hg) in response to single injections of nor-epinephrine. N: Normal; A: adrenalectomized dogs.

ectomized animal under stress cannot properly redistribute blood because of the relative ineffectiveness of noradrenalin in reflex vasoconstriction. The C-11 oxysteroids seem to be necessary for the proper degree of vascular response even though these substances are themselves ineffective as vasoconstrictors.

The further analysis of the inter-relationship between the C-11 steroids and vasomotor activity necessitated a different methodologic approach. The experiments about to be reported were done on rats with the Chambers-Zweifach mesoappendix preparation, chosen as a method for

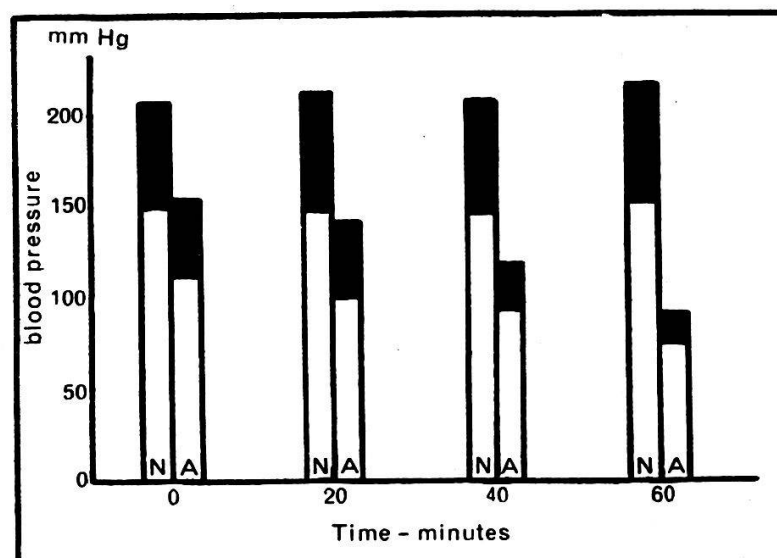


Fig. 6. Response of blood pressure to repeated injections (at 20-minute intervals) or $1 \mu\text{g}$ nor-epinephrine/kg body weight. Unshaded areas represent base levels of pressure. Shaded areas represent rise above base levels. N: Normal; A: adrenalectomized dogs. (From Amer. J. Physiol. 165, 450 [1951].)

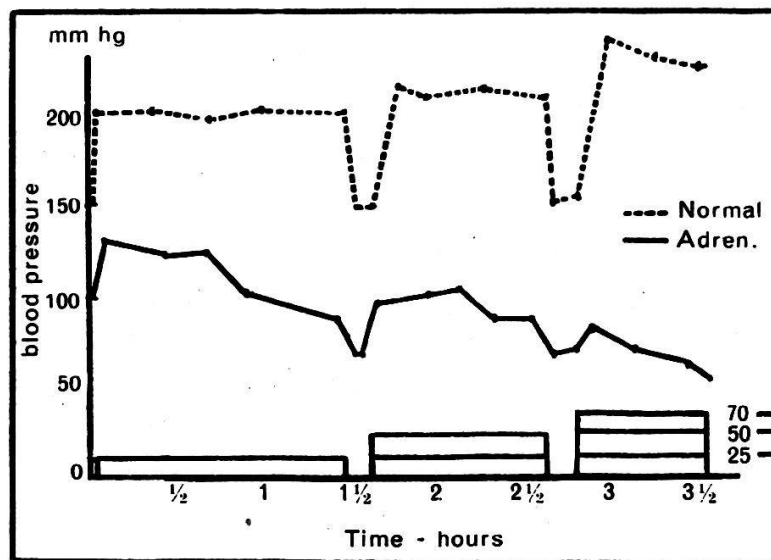


Fig. 7. Blood pressure response to continuous intravenous infusion of nor-epinephrine at rates of 25, 50 and 70 $\mu\text{g/kg/h}$ as indicated by scale on the right. Resting normal and adrenalectomized dogs. (From Amer. J. Physiol. 165, 450 [1951].)

the more intimate study of the responses of the splanchnic bed to various pharmacologic agents.

The method used consists in exteriorizing the portion of the gut containing the mesoappendix and placing this little mesenteric fold in position for microscopic observation. The field is irrigated by a continuous flow of a warm Ringer's solution containing gelatin. Under these conditions observation can be made of the state of the vessels, the speed of blood flow, damage to vessel walls, hemorrhage, and other changes.

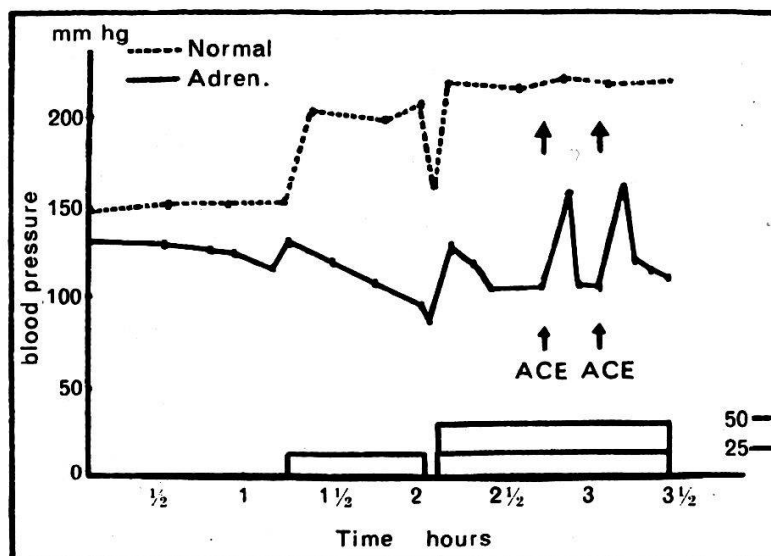


Fig. 8. Effect of single intravenous injections of 20 cm^3 ACE on blood pressure response to continuous infusion of 25 and 50 μg of nor-epinephrine/kg/h, as indicated by scale on the right, in working normal and adrenalectomized dogs. (From Amer. J. Physiol. 165, 450 [1951].)

It is, of course, easily possible to observe the reaction of such a vascular bed to drugs given parenterally or applied topically.

In the normal rat there occurs the phenomenon called vasomotion, which consists of alternate constriction and relaxation of the arterioles and metarterioles. When 0.02 cm³ of a 1:800,000 solution of noradrenalin is applied topically, there is a very sharp vasoconstrictor response, with momentary stoppage of flow, and an equally brisk recovery to the initial state. Such an application can be repeated every ten or twenty minutes for hours with equivalent results. That is, the sensitivity of the normal blood vessels to this drug remains the same even after hours of exposure of the normal mesoappendix. A parenteral injection of 0.3 cm³ of 1:1000 noradrenalin causes prolonged constriction. Complete recovery occurs, however, and no residual change can be seen in the field of observation (11, 12).

The adrenalectomized DOCA-treated rat in good clinical condition, maintaining a normal electrolyte balance, behaves in an entirely different manner. The initial sensitivity to noradrenalin is like that of the normal, but with time there is an increasing resistance to the drug, so that after one or two hours of observation, from ten to fifteen times the initial effective dose is necessary to produce local constrictive effects. Obviously, the experimental procedure itself represents a «stress», and the behaviour toward noradrenalin is analogous to the course of events in the adrenalectomized dog under the stress of muscular exercise (fig. 9). A large parenteral dose of noradrenalin will produce constriction but the recovery phase is poor and diapedesis and hemorrhage can be seen to occur. The topical application of small amounts of ACE (but not of DOC-glucoside) restores the sensitivity to topical noradrenalin within 15 or 20 minutes. The effect of the adrenal steroids is local, and these steroids by themselves do not have any vasoconstrictor action. Obviously, therefore, the C-11 oxysteroids have to be present for the effector portions of the small vessels to be able to respond to noradrenalin (11, 12). The immediate response of the vessels of the mesoappendix to the vasodilating effect of acetylcholine and histamine does not seem to be altered by the absence of C-11 oxysteroids.

In succeeding experiments, a more acute stress situation was produced by the subcutaneous injection of 0.3 cm³ of a 4% formalin fixative solution. Within 15 or 20 minutes intense activity could be observed in the mesoappendix preparation: vasoconstriction, cessation of blood flow, localized dilatations of arterioles and venules, diapedesis, and hemorrhage. Death occurred approximately one hour after the administration of formalin. The control group of normal animals showed no vascular

reaction whatever to this dosage of formalin and all survived. Because the vascular picture produced in the formalin experiments was similar to the reaction seen in the adrenalectomized rat given a large parenteral dose of noradrenalin, it was postulated that the formalin effect was mediated by the secretion of sufficient noradrenalin to produce constriction but with poor recovery. Accordingly, dibenamine was administered to adrenalectomized rats prior to the formalin stress. Dibenamine completely prevented the vascular damage that otherwise followed formalin injection. Dibenamine also prolonged the survival time of adrenalectomized rats in which stress was produced by formalin administration (11-13).

These studies (8-13) and others now in progress do not yet permit us to draw a clear-cut picture of the relation of C-11 steroids to autonomic effector agents. They do, however, indicate that an intimate functional relationship exists, so far as blood vessels are concerned, between physiologic vasoconstriction, recovery from such vasoconstriction, and the presence or absence of the C-11 oxysteroids. The vascular bed responds poorly to the demands imposed by the stress and recovers poorly or not at all from bombardment by the autonomic system. The end result is peripheral vascular collapse.

The results obtained support the following view of the phenomenon of stress and its consequences. In the normal animal, a stress stimulus (such as cold, heat, muscle exertion, drugs, etc.) sets up a train of im-

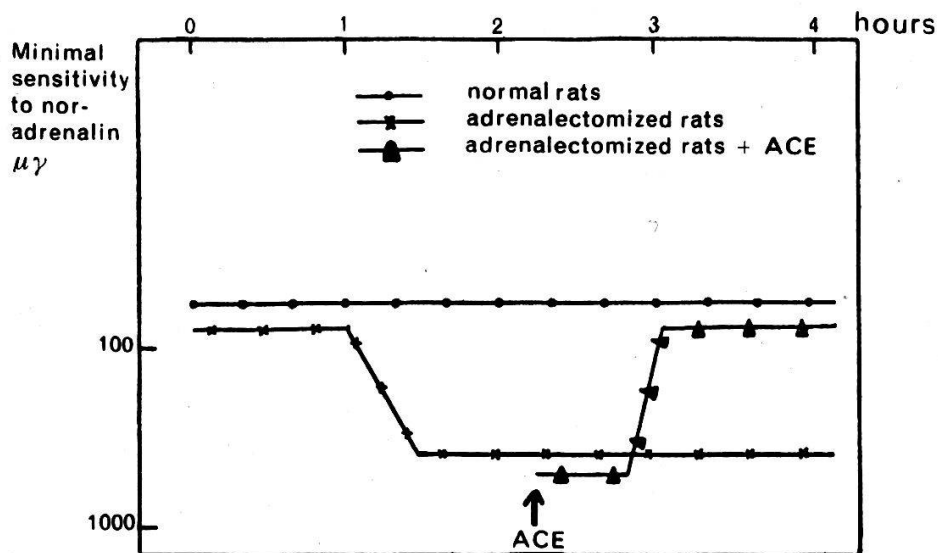


Fig. 9. Comparison of sensitivity of mesoappendix blood vessels in normal and adrenalectomized rats to nor-adrenaline with time. Note logarithmic ordinates. Graph represents a composite of experiments on 25 normal and 13 adrenalectomized rats. None of the 6 adrenalectomized rats which did not receive ACE (Wilson's aqueous adrenal cortical extract) spontaneously regained sensitivity with time. (From Amer. J. Physiol. 165, 456 [1951].)

pulses which reach various areas in the central nervous system. As a result of this bombardment, two main pathways are stimulated. One excites the anterior pituitary gland to the liberation of ACTH and thus the adrenal cortex is stimulated. The other pathway which is excited by stress is the vast network of the autonomic nervous system. The autonomic neurohumours have pronounced actions on the state of the small blood vessels. In the presence of adrenal cortical hormones, the blood vessels react in a well-coordinated fashion to the «autonomic» substances. In the absence of sufficient cortical hormones, the small blood vessels react poorly to the same substances, with the result that contraction and dilatation of blood vessels occurs haphazardly, and is not coordinated with the needs of various portions of the body. The beneficial effect of cortical hormones seems to be exerted directly in the area of the small blood vessels and not through the mediation of any so-called «metabolic effect» on the body as a whole.

It has been finally possible to show that the adrenalectomized animal may be protected from certain stresses and survive them as well as does the normal, by the use of drugs which block the action of the autonomic effector substances or which prevent their production (dibenamine, atropine, banthine, etc.).

We are in the process of examining which actions of the adrenal cortical hormones can be connected with the relationship we have demonstrated between these hormones and the effector substances of the autonomic nervous system.

This point of view may of course not hold for some or many of the actions of the adrenal cortical substances.

However, we are following our working hypothesis «parce qu'une hypothèse proprement utilisée montre la direction au travail scientifique».

I should like to acknowledge the participation of the following members of my laboratory in this work: Drs. *J. Fritz*, *M. S. Goldstein* and *E. R. Ramey*.

1. Rheumatoid Arthritis Research Group, Michael Reese Hospital, «Use of ACTH and Compound E in Rheumatoid Arthritis and other Disorders», *Progress in Clinical Endocrinology*, S. Soskin, Ed., New York, Grune & Stratton, 1950, pp. 589. – 2. *Taubenhaus, M.*, and *Amromin, G. D.*: *Endocrinol.* **44**, 359 (1949). – 3. *Taubenhaus, M.*, and *Amromin, G. D.*: *J. Labor a. clin. Med. (Am.)* **36**, 7 (1950). – 4. *Ingle, D. J.*, and *Lukens, F. D. W.*: *Endocrinol.* **29**, 443 (1941). – 5. *Ingle, D. J.*: *Endocrinol.* **31**, 419 (1942). – 6. *Ingle, D. J.*: *Proc. Soc. exper. Biol. a. Med. (Am.)* **44**, 450 (1940). – 7. *Ingle, D. J.*: *Amer. J. Physiol.* **129**, 278 (1940). – 8. *Ramey, E. R.*, *Goldstein, M. S.*, and *Levine, R.*: *Amer. J. Physiol.* **162**, 10 (1950). – 9. *Goldstein, M. S.*, *Ramey, E. R.*, and *Levine, R.*: *Amer. J. Physiol.* **163**, 561 (1950). – 10. *Ramey, E. R.*, *Goldstein, M. S.*, and *Levine, R.*: *Amer. J. Physiol.* **165**, 450 (1951). – 11. *Fritz, I.*, and *Levine, R.*: *Amer. J. Physiol.* **163**, 713 (1950). – 12. *Fritz, I.*, and *Levine, R.*: *Amer. J. Physiol.* **165**, 456 (1951). – 13. *Ramey, E. R.*, *Fritz, I.*, *Goldstein, M. S.*, and *Levine, R.*: *Feder. Proc.* **10**, 108 (1951).

Discussion:

A. Jung (Zürich): Auf Grund unserer umfassenden Untersuchungen an über 30 Patienten mit primär chronischer Polyarthrititis kann ich die Ergebnisse, über die uns Herr *Levine* berichtete, nur bestätigen. Wir fanden keinen Faktor, der auf Cortison- oder ACTH-Therapie hin eindeutig verändert wurde. Die Patienten mit primär chronischer Polyarthrititis zeigen alle eine sehr große Labilität, die sich aber nicht bei allen Patienten an den gleichen Systemen äußert. Wir haben darüber in der *Schweiz. med. Wschr.* (39, 937 [1951]) berichtet. Wir müssen darnach trachten, diese Labilitäten auszugleichen. Cortison und ACTH helfen uns oft dabei, sie können aber auch umgekehrt die Labilitäten vermehren. Dann kann zunächst der Gelenkzustand gut bleiben, der Allgemeinzustand sich aber verschlechtern, oder es verschlechtert sich auch der Gelenkzustand unter Cortison oder ACTH-Einwirkung. Dies ist besonders nach Röntgenbestrahlung der Fall. Dann müssen diese Hormone abgesetzt werden, bis eine gewisse Beruhigung eingetreten ist. Nachher wirken sie wieder gut. Cortison und ACTH sind also Substanzen, die nicht an sich die primär chronische Polyarthrititis heilen, sondern nur dann, wenn der Körper zu einer entsprechenden Regularisation bereit ist. Das muß durch andere Maßnahmen unterstützt werden. Es scheint mir sehr wichtig zu sein, daß vor allem die kleinen Gefäße und das vegetative Nervensystem mit seinen Effektoren von Herrn *Levine* in den Vordergrund gerückt wurden.

G. Sala (Milano): Cavallero, Ballabio and myself have studied the influence of Cortisone on blood pressure. In our experience Cortisone sometimes increased the blood pressure in man (100 mg daily for 10–20 days) and increased it constantly in the rat (5 mg daily for 20 days).

Plasma volume and cardiac output did not increase; sodium retention was not constant and it was not connected with the rise of blood pressure; no characteristic pattern of Ecg were present. In the rat no histological lesion was present in the kidney which might account for the hypertension and in man renal functions were increased by Cortisone treatment. Then, according to Dr. *Levine*, we have postulated that Cortisone might provoke hypertension by sensitizing peripheric vessels to sympathetic hypertensive stimuli.

F. Gross (Basle): There is a publication by *Meier and Bein* (*Helv. Physiol. Acta* 8, 436 [1950]) which shows that in cats the increase in femoral arterial blood flow which occurs under normal conditions after injection of small doses of Adrenalin is diminished or even reversed, resulting in a decrease after removal of the adrenals. Infusion of small amounts of noradrenalin, which are without effect on the blood pressure, restores the former type of vascular reaction. It was concluded from this that the adrenals discharge substances (noradrenalin and perhaps also certain cortical steroids) responsible for the type of vascular reaction found after injection of adrenalin and other vasoactive substances.

B. N. Halpern (Paris): Dr. *Levine* produced evidence to prove that adrenalectomised dogs are much more sensitive to any kind of shock, and that their vasomotor system seems to become unadapted by this operative procedure. It should be noted that the adrenals contain two glands; and the role of the medullary hormone in the adjustment of the circulatory equilibrium in sudden modification of blood pressure should not be overlooked. We have found that adrenalectomy considerably increases the toxicity of histamine in mice. If the average lethal dose of histamine is 50 mg/20 g in normal mice, this dose drops to 0.5 mg/20 g in adrenalectomised animals. Adrenaline increases the resistance of adrenalectomised mice to histamine by about 10 times, while DOCA does not change the tolerance to histamine. Promethazine, which does not modify the toxicity of histamine in normal mice, raises the tolerance to histamine of adrenalectomised mice to that of normal animals. Cortisone alone increases the tolerance of the adrenalectomised mouse to histamine by about five times. But cortisone administered together with adrenaline, raises the sensitivity of the adrenalectomised

animal to that of the normal one. Our research has shown that adrenalectomy has rendered the vascular bed of mice more sensitive to the angiotoxic effect of histamine, as proved by the degree of hæmoconcentration.

Thus cortisone, adrenaline and certain antihistamines, which increase the tolerance of the adrenalectomised animal to histamine, seem to exert this effect by increasing the resistance of the small vessels to the angiotoxic effect of histamine.

B. N. Halpern and D. R. Wood: Brit. J. Pharmacol. 1950, Vol. 5, 510.