The Canadian Medical Association Journal

Vol. 43 TORONTO, JULY, 1940 No. 1

ON THE THERAPEUTIC VALUE OF ADRENAL CORTICAL HORMONES IN TRAUMATIC SHOCK AND ALLIED CONDITIONS*

BY HANS SELYE, CHRISTIANNE DOSNE, LUCY BASSETT AND JOAN WHITTAKER

Montreal

A FEW years ago we observed that animals exposed to various damaging agents respond with a syndrome which we termed the "alarm reaction", since we believed it to represent the somatic expression of the call to arms of the body's defense forces. This syndrome is characterized by manifold degenerative lesions and biochemical changes such as are typical of shock, but in addition to these we also noticed changes which were interpreted as signs of defense against shock.[1, 2, 3] Since upon exposure to a noxious agent signs of damage and of defense usually appear conjointly, it seemed difficult to prove whether any particular change represents shock or a reaction against shock. The fact that a satisfactory definition of "shock" has still not been given added to this difficulty, but for our purpose we feel that if the term shock is to be retained it should be used in its original meaning, designating merely a condition of suddenly developing general damage. Later work showed that if we accept this definition of shock the symptom-complex of the alarm reaction may be divided into two different periods or phases. The first of these is the phase of shock. This is characterized by loss of muscular tone, decrease in body temperature, decrease in blood volume with transudation of plasma into the tissue spaces, anuria, a rapid fall in blood chlorides and often also in blood sugar, hæmorrhages into the gastro-intestinal tract, and other changes, all of which are generally accepted as typical of shock. During this stage the organism is obviously damaged and many experimental animals die. The duration of this shock phase depends on the severity of the agent used and on the resistance of the animal, and varies between one and thirty-six hours in the rat. Immediately following this stage an entirely different set of symptoms appears which might descriptively be referred to as "countershock". During this second phase the most outstanding morphological changes are marked enlargement of the adrenal cortex, severe atrophy of the thymus and to a lesser degree of other lymphatic organs. Most of the changes characteristic of shock have not only disappeared but are actually reversed during the countershock period. Thus the blood chlorides and the blood volume tend to rise above normal, diuresis is excessive, and the temperature rises. Since adrenalectomized animals are unable to develop a clear cut countershock response and at the same time show a very low resistance against damaging agents, and since the adrenals reveal obvious signs of increased activity, especially during the countershock phase of the alarm reaction, we concluded that the adrenals play an important rôle in shock defense.[4, 5, 6, 7]

Although previous investigators described most of the morphological changes characteristic of traumatic shock in great detail they neglected the adrenals, and Moon[8] in his excellent monograph on shock states merely that "The adrenals participate in the capillary congestion seen elsewhere but they show no other changes". Our observations in the rat[1, 2] indicated however that in traumatic shock the adrenals always show characteristic changes. The cortical cells discharge their lipid granules (probably the carriers of the cortical hormones) and become greatly enlarged. Mitotic proliferation of these cells is likewise not uncommon, and as a result of these changes the

* From the Department of Anatomy, McGill University, Montreal.

weight and size of the glands is greatly increased. The adrenal medulla loses its chromaffin granules, which is taken to indicate that it discharges adrenaline into the blood. These changes were observed following all types of surgical injuries such as extended skin lesions, bone fractures, peritoneal lesions etc. It was noted, further, that following other types of injuries, such as excessive muscular exercise, exposure to cold, or treatment with toxic doses of various drugs, the adrenals show the same histological changes as are seen in cases of traumatic shock. Following all these injuries the more the adrenals enlarge, the more pronounced is the thymus involution. This led us to conclude that excessive adrenal activity and thymus involution are both parts of the same general defense reaction against damage, namely, the "alarm reaction". The fact that in adrenalectomized animals, which develop all other signs of shock very readily, the thymus fails to involute during exposure to stress and strain gave further support to our contention that the adrenal enlargement and the thymus atrophy are countershock phenomena. The question arose, however, what part of the adrenal is essential for shock defense? Cannon's well known work on the emergency secretion of adrenaline during exposure to damage made it rather likely that this hormone is the one which is primarily involved in countershock phenomena. Certain other facts known at that time pointed in the same direction. Thus Kellaway and Cowell[9, 10] noted that in adrenalectomized cats, which are very sensitive to histamine, resistance against this compound is greatly improved by adrenaline administration. Perla and Marmorston-Gottesman[11, 12] stated that both adrenaline and cortin are capable of raising histamine resistance in the adrenalectomized rat. Wyman[13] confirmed the increased histamine resistance of adrenaline treated adrenalectomized rats and stated that the presence of large quantities of extra-adrenal chromaffin tissue protects against histamine, while accessory cortical tissue and cortical transplants have no beneficial effects. He concluded that, at least in the case of histamine resistance, the increased sensitivity following adrenalectomy is due to medullary deficiency. This assumption received further support through the experiments of Ingle[14] who found that adrenaline increases the histamine resistance of rats without adrenal medulla, while simultaneous treatment with cortin causes no further increase. Our own experiments indicated, however, that even lethal doses of adrenaline fail to cause thymus involution in the adrenalectomized rat, while cortin given in sufficiently large doses is effective in this respect. It was observed, further, that the toxic effects of adrenaline are counteracted by cortin in the adrenalectomized rat.[1] These experiments confirmed our belief that it is primarily an increased adrenal cortical secretion which is responsible for the development of resistance in the countershock phase.*

Since the cortin content of body fluids is too low to be estimated by the ordinary methods of bio-assay, Selye and Schenker[15] worked out a particularly sensitive assay technique suitable for such purposes. Using this method, Weil and Browne[16, 17] showed that following major surgical interventions the cortin excretion in the urine is greatly increased. This is another significant observation supporting the conception that increased cortin production is an important part in the physiological countershock phase of the alarm reaction.

Numerous clinical observations purporting to show an increase in the general resistance of the organism due to treatment with adrenal cortical preparations have also been published, especially during the last few years. Thus it was claimed that such therapy is beneficial in Graves' disease,[18, 19, 20] muscular dystrophy and other conditions of asthenia,[18, 20 to 24] Paget's disease,[24] intestinal intoxication,[23] hæmorrhage,[23] allergic conditions,[26] various infectious diseases,[26 to 33] burns,[34] pregnancy toxicosis,[35] obstetrical shock[36] and surgical shock.[37 to 40] However, as far as the treatment of shock and allied conditions is concerned, the value of cortin therapy failed to receive general recognition, probably because many of these authors advocated the use of desoxycorticosterone, which, as we shall see later, is relatively inactive in this respect. Others used crude extracts which could not have contained much if any of the active cortical material, as judged

* Since this manuscript was completed several investigators called attention to the fact that our work on the alarm reaction is definitely indicative of the existence of a relative adrenal cortical insufficiency in cases of shock and emphasized that on the basis of our experiments, clinical administration of cortin would seem promising in wound shock (Varangot, J., *La Presse Médicale*, 1940, **48**: 103; Editorial in *The Lancet*, March 23, 1940, p. 555; Pollak, H., *The Lancet*, March 23, 1940, p. 574).

by the method of preparation. Further, in most cases, and this includes all publications on traumatic shock, in addition to cortin several other therapeutic measures were employed so that it is difficult to evaluate the results obtained. Another confusing factor in all these clinical observations is the impossibility of securing really adequate control cases.

The fact that general resistance is low after adrenalectomy and is increased by cortin has been observed by a great many investigators in well controlled animal experiments, but this did not prove that the adrenal is specifically involved in shock resistance, since removal of any gland which plays an important rôle in the maintenance of normal metabolism (*e.g.*, the pituitary, thyroid, parathyroids, pancreas, etc.) decreases general resistance, while restoration of metabolic equilibrium by suitable substitution therapy results in normal resistance. It seemed particularly important, therefore, to show that cortical preparations can increase resistance above the normal level in the non-adrenalectomized animal. It was of special interest, therefore, when Parkins *et al.*[41] not only confirmed our experiments concerning the increase in adrenaline-resistance obtained by cortin treatment in adrenalectomized animals but were able to extend these findings to normal dogs. The fact that cortin antagonizes both insulin hypoglycæmia and adrenaline hyperglycæmia[42] in the rat furnished another proof that cortical hormone acts as a "stabilizer" of metabolic processes even in the non-adrenalectomized animal.

In this connection the recent work of Maddaloni[43] deserves to be mentioned. This author obtained increased resistance against exposure to heat in rabbits treated with cortin. Perla *et al.*[40] published well controlled experiments in rats indicating that both cortical extracts and desoxycorticosterone raise histamine resistance, especially if such treatment is combined with the administration of large doses of saline solution. In view of what has been said above it would not be justified, however, to assume that improvement of histamine resistance means an improvement in "shock resistance". Adrenaline likewise proved very active in counteracting histamine, while most investigators agree that it is inactive as a therapeutic agent in shock. It has also been reported that in animal experiments cortin exerts a beneficial effect in anaphylaxis,[44] intoxication due to intestinal obstruction,[45, 46] asphyxia,[47] or intoxication with acetonitril,[48] iodo-acetic acid,[49] potassium,[31, 50] and numerous other drugs.

The fact that cortical hormone therapy exerts beneficial effects in so many different conditions makes it rather likely that the hormone is not a specific antidote in any one of these cases but raises shock resistance in general because a condition of "relative adrenal insufficiency" exists in organisms exposed to non-specific damage. The clinical observations concerning the curative action of cortin in surgical shock likewise appeared to point in this direction, but in patients suffering from shock cortin has so far never been used without the simultaneous administration of other therapeutic agents, and no animal experiments have yet been published on the action of cortin in surgical shock. It was felt desirable therefore to study the action of this hormone in a pure type of shock relatively uncomplicated by specific pharmacological effects.

Since partial hepatectomy is a surgical intervention which leads to definite signs of shock the extent of which may be carefully gauged by always removing the same amount of liver tissue, we used this as a method for the production of shock, and found that suitable cortin therapy prevents the hypochloræmia, and the decrease in blood volume and in blood sugar which are usually elicited by this intervention. In this series of experiments it became obvious that one of the most important factors to consider in the cortin treatment of shock is to subdivide the total amount of hormone given and to administer it in frequently repeated small doses.[51] The great efficacy of this type of treatment had already been recorded in one of our previous communications.[1]

In the present communication we wish to report on a series of animal experiments which we believe give definite evidence that cortin treatment is of great value in combating surgical shock and allied conditions. These experiments led us to the conclusion that the method of administration is a very important factor, and that the numerous and rather inexplicable failures which both we and other investigators encountered must at least in part be ascribed to the fact that such treatment is ineffective unless sufficiently large doses of suitable cortical ster-

oids are administered at the right time during the evolution of the shock syndrome.

METHODS

In our first experiments we attempted to pretreat our experimental animals with cortin or desoxycorticosterone acetate in the hope that "saturation" of the organism with cortical substances would yield the best results. This proved to be erroneous, probably because such treatment leads to atrophy of the adrenal cortex within a few days. Since, on the other hand, cortin has only a very transitory effect a cumulative action or "saturation" is not to be expected. We therefore proceeded to use the method of continuous hormone administration at short intervals after exposure to the shock-producing agent. The cortin preparation used was Wilson's cortical extract which contains one rat unit as defined by Selye and Schenker[15] in 0.01 to 0.03 c.c., depending on the batch used. In order to produce shock we availed ourselves of two different methods. One of these consisted in the administration of repeated subcutaneous injections of a 4 per cent formaldehyde solution, a procedure which corresponds to a chemical tissue damage owing to the protein-precipitating effect of the formaldehyde. This permits the production of a well controlled degree of tissue destruction and damage, and is preferable for many reasons to the mechanical traumatization of tissues which produces a condition complicated by varying degrees of hæmorrhage and which is difficult to control with regard to the severity of the resulting shock. The second method employed consisted in crushing the stomach, the duodenum, and the cæcum five times each with a small hæmostat. This led to severe and often fatal shock, but was frequently complicated by hæmorrhages into the intestine. In order to get objective indices of the degree of shock, the blood sugars have been determined by the Hartmann-Schafer-Somogyi method and the whole blood chlorides by the van Slyke method. The latter are expressed in mg. per cent NaCl. Hæmoglobin determinations were performed with Evelyn's photo-electric colorimeter. The blood volume was estimated by the method employed in our previous publications.[51] The significance of the apparent differences between the cortin-treated and the untreated animals was evaluated by "Student's" method for small samples, and is expressed in terms of probability estimated by graphic interpolation in Fisher's table of t.[52] It is generally agreed that differences may be regarded as significant if P is smaller than 0.05. In most of our work rats were used as experimental animals, although in a few cases we confirmed our main findings in rabbits, cats and guinea pigs. Weil *et al.*,[53] who worked on this problem simultaneously with us, are publishing a detailed report of their observations on the prevention of surgical shock by cortical substances in rabbits.

EXPERIMENTAL FINDINGS

In our first experiment twelve female albino rats weighing 166 to 210 g. received three times 0.3 c.c. of a 4 per cent formaldehyde solution subcutaneously within twenty-four hours. During this period the animals were fasted in order to prevent any complication through individual variations in food intake. Six of these animals were given eight subcutaneous injections of 0.25 c.c. of cortin distributed throughout this period. All the rats were sacrificed one hour after the treated group received its last cortin injection. At this time the treated animals were definitely in a better condition than the controls. Their blood chlorides averaged 342 mg. per cent, their blood sugar 85 mg. per cent, and their hæmoglobin 17.8 g. as compared with 319 g. per cent, 70 mg. per cent and 20.4 g., respectively, in the untreated controls. Statistical analysis of these data indicates that $P =$ 0.04 for the chlorides, 0.01 for the sugar, and less than 0.01 for the hæmoglobin. That is to say, the hypochloræmia, hypoglycæmia, and the hæmoconcentration which are characteristic of shock in the rat were significantly counteracted by cortin. A repetition of this experiment with ten injections of 0.5 c.c. of cortin and four times 0.3 c.c. of formaldehyde on six experimental and six control female rats weighing 178 to 210 g. led to essentially the same results. In the cortin-treated group the average blood chloride value was 391 mg. per cent and the blood sugar 83 mg. per cent, while in the rats receiving formaldehyde only the corresponding values were 366 mg. per cent and 67 mg. per cent, respectively. $P = 0.03$ both for the chlorides and for the sugar. Since in these somewhat larger animals hæmo-concentration judged by the hæmoglobin was not very marked the difference in this value between cortin and control animals was not significant.

Numerous other similarly conducted experiments yielded the same results, and may there-

fore be omitted here. We wish to describe only one more experimental series of this group, since it shows the relative inactivity of desoxycorticosterone, a substance which has been recommended for the purpose of combating shock. Eighteen female albino rats weighing 148 to 209 g. were divided into three groups of six in such a manner that the average body weight was 180 g. in each group. Shock was produced in all these animals by the administration of four injections of 0.3 c.c. of 4 per cent formaldehyde subcutaneously during a twenty-four hour fasting period. One group remained otherwise untreated, serving as a control; the second group received ten subcutaneous cortin injections each of 0.5 c.c.; and the third three subcutaneous injections of desoxycorticosterone acetate each containing 0.5 mg. of the substance dissolved in 0.2 c.c. of peanut oil. The results of this experiment are summarized in the following table:

Treatment	*Formaldehyde*	*Formaldehyde and desoxycorticosterone*	*Formaldehyde and cortin*
Blood sugar	64 mg. %	69 mg. % (P=0.3)	81 mg. % (P=less than 0.01)
Blood chlorides	330 mg. %	331 mg. % (P=0.9)	397 mg. % (P=less than 0.01)
Hæmoglobin	20.8 g. %	18.8 g. % (P=0.1)	17.2 g. % (P=less than 0.01)

This table shows that while the beneficial effect of cortin is obvious and yields highly significant data no statistically significant inhibition of the objective signs of shock was obtained by desoxycorticosterone acetate.

In the case of continued treatment with high doses of desoxycorticosterone the substance proved not only inactive but actually harmful. Thus in an experiment on female albino rats weighing 93 to 126 g. we treated one group of six animals with 6 mg. of desoxycorticosterone acetate dissolved in 0.2 c.c. of peanut oil during a period of nine days, after which surgical shock was produced by crushing of the intestines as described above. Food was withdrawn after the operation. Eight controls were damaged in exactly the same manner but received no treatment. At the end of twenty-four hours only 3 of the controls died, while in the desoxycorticosterone-treated group 5 animals succumbed. In another experiment 8 male and 8 female albino rats weighing 100 to 150 g. were first treated with 0.1 c.c. of 4 per cent formaldehyde twice daily, the dose being gradually raised to 0.3 c.c. thrice daily within sixteen days. A similar control group received exactly the same formaldehyde treatment but in addition to this 5 mg. of desoxycorticosterone acetate twice daily subcutaneously in 0.2 c.c. of peanut oil. By the end of the sixteenth day 5 of the desoxycorticosterone animals died while the rats receiving only formaldehyde all survived. It may incidentally be mentioned that although such large doses of formaldehyde inhibit growth they cause an increase in weight because of the subcutaneous œdema which is formed at the site of the injection. As a result of this the controls gained an average of 28 g. while the desoxycorticosterone treated animals showed huge subcutaneous water accumulations resulting in an average weight increase of 60 g.

In agreement with what we said above, we feel that the probable cause of these untoward effects of desoxycorticosterone is that it causes marked hypochloræmia and adrenal cortical atrophy, as shown by Selye and Dosne.[51] This effect interfered with the normal adrenal cortical enlargement which is usually produced by exposure to damaging agents. Thus, in the first among the above-mentioned experiments the average adrenal weight increased from a normal of 45 mg. to 51 mg. under the influence of surgical shock, while in the group exposed to the same amount of surgical injury but treated with desoxycorticosterone the average adrenal weight was only 30 mg. Similarly, in the formaldehyde experiment the average adrenal weight increased under the influence of this drug from 39 to 46 mg., while the animals receiving desoxycorticosterone as well as formaldehyde had adrenals which were actually subnormal in weight, averaging only 33 mg. It seems that although such high doses of this compound as have been given in the above-mentioned experimental series are unable to raise resistance, they inhibit the normal compensatory enlargement of the adrenals, and thus actively interfere with the physiological defense mechanism against damage. We feel that these experiments should be interpreted as a warning against prolonged pre-treatment with this substance in preparation for a surgical intervention.

Even in acute experiments desoxycorticosterone acetate proved to interfere with the normal adrenal response. Thus, in a group of six male albino rats weighing 170 to 250 g. the intestines were crushed in the usual manner and the animals were sacrificed twenty-four hours later. The average adrenal weight increased from the normal of 33 to 49 mg. Another group of six rats of the same size received 0.5 c.c. of propylene glycol containing 5 mg. of desoxycorticosterone acetate intravenously immediately after their intestines were crushed as in the previous group. In these animals the average adrenal weight remained practically unchanged during the twenty-four hours after the operation, the average being 34 mg. Although the injury was not sufficiently severe to kill any of these relatively large rats the treated animals appeared to be in a less satisfactory condition than the untreated ones, which may perhaps be regarded as a result of the inhibitory action exerted by the desoxycorticosterone on the adrenals.

Since our experiments with pre-treatment were highly unsatisfactory the question arose whether administration of the more active cortin in a single large dose immediately after the first treatment with the shock producing agent gives as satisfactory results as the technique of repeated injections which we generally follow. For this purpose a group of eighteen albino female rats weighing between 140 and 165 g. were divided into three groups of six, each having an average weight of 140 g. All groups were given four subcutaneous injections of 0.3 c.c. of the 4 per cent formaldehyde solution during a twenty-four hour fasting period. The first group received no other treatment, the second group was given a single injection of 4.0 c.c. of cortin immediately after the first formaldehyde injection, while the third group received the same amount of cortin in eight subcutaneous injections of 0.5 c.c. throughout the period of observation. In these relatively young rats the blood sugar response to formaldehyde was extremely irregular as it usually is at this age. As a result of this no significant effect was exerted by cortin in this respect in either group. It was observed, however, that the blood chlorides averaged 378 mg. per cent in the first, 373 mg. per cent in the second, and 401 mg. per cent in the third group. The blood volume was 1.15, 1.7 and 1.9 c.c. and the hæmoglobin 17.6, 18.3 and 16.1 on the average in the three groups respectively. This indicates clearly that cortin given in a single injection is much less effective than if administered in divided doses.

As we said above, traumatic shock produced by mechanical means is rather difficult to gauge with regard to its intensity, and was therefore considered less suitable for routine investigations of the optimum conditions of treatment. Yet it was felt that such experiments should be performed in order to establish beyond doubt that cortin given in divided doses is of value in the treatment of traumatic shock as it usually occurs. For this purpose numerous experiments have been performed in rats, and a few in rabbits, cats and guinea pigs. All of these indicated that cortin is beneficial if given in divided doses, while little, if any, benefit was derived from single large injections of cortin or from desoxycorticosterone given either in single or in divided doses. In order to save space we shall merely report on one experiment which is representative of this whole series. Twelve female albino rats weighing 130 to 165 g. were divided into two groups, each of which had an average weight of 145 g. In all animals severe surgical shock was produced by the technique described above. One group received no other treatment, while the second was given eight subcutaneous cortin injections each of 0.5 c.c. during a twenty-four hour fasting period. The results are summarized in the following Table:

Treatment	*Intestinal trauma*	*Intestinal trauma and cortin*
Blood chlorides	433 mg. %	470 mg. % (P=less than 0.01)
Blood volume	2.0 c.c.	2.5 c.c. (P=0.07)
Hæmoglobin	11.5 g. %	10.1 g. % (P=0.2)

In evaluating these results it must be kept in mind that the accompanying hæmorrhage causes blood dilution with the consequent marked drop in hæmoglobin and an increase in whole blood chlorides, both of which are only partly compensated by the blood-concentrating action of shock. Yet just as in our previous experiments on the shock caused by partial hepatectomy, formaldehyde injections, etc., cortin tends to counteract the blood chloride decrease which is so characteristic of shock.

The blood sugar variations were always so excessive in the animals in which shock was produced by intestinal manipulation that cortin treatment did not yield conclusive results. The blood dilution was usually better after treatment though this was likewise not always significant.

We should comment on the fact that in all these experiments the action of cortin was studied with respect to its effect on the laboratory indices of shock rather than on its clinical symptoms. The reason for this is that the former give much more objective criteria. In a few experimental series, however, we continued the experiment until the animals either died or completely recovered from shock. We must admit that in these experiments the action of cortin was less obvious. Still in many cases we noted that among the animals treated with divided doses of cortin, a larger proportion survived than among the untreated ones. The following are typical examples of this series. In a group of 16 male albino rats weighing 150 to 210 g. in which surgical shock was produced by crushing the intestines as described above 8 animals were treated with 4 c.c. of cortin administered in eight subcutaneous injections within the first twenty-four hours after the surgical intervention, while the remaining 8 served as controls. Five of the controls died within thirty-six hours and 3 recovered, while in the cortin-treated series, only 2 died and 6 recovered. In a second similarly conducted experiment, 6 out of 8 untreated animals, and only 3 out of 8 cortin-treated ones succumbed.

SUMMARY AND CONCLUSIONS

Our experiments indicate that following recovery from exposure to damaging agents which elicit symptoms of shock one notices a defence reaction which may be termed "countershock". During this reaction many of the symptoms and signs of shock are actually reversed. Shock and countershock constitute the two characteristic phases of the so-called "alarm reaction", that is to say, the physiological response of the body to damage as such.

During the countershock response the adrenal cortex shows signs of increased hormone production, and in adrenalectomized animals which are very sensitive to diverse noxious agents a characteristic countershock response fails to develop. Cortin-treated adrenalectomized animals on the other hand are relatively resistant to noxious agents and respond with typical countershock phenomena. However, more cortin is needed for shock resistance than for maintenance of life under normal conditions. These observations led us to conclude that increased cortin production plays an important rôle in shock resistance, and that the symptoms and signs of shock are at least in part due to a relative adrenal insufficiency.

In an effort to imitate the physiological countershock phenomena we administered large doses of cortin to rats in which damage was produced by diverse means, and found such treatment to be highly effective in counteracting the objective signs of shock. In this respect a single large amount of cortin, given at the time when shock begins to develop, is considerably less effective than the same quantity administered in many divided doses. Prolonged pretreatment with cortical preparations causes severe adrenal cortical atrophy. Since, on the other hand, continued treatment with such preparations leads to no cumulative effect such pre-treatment is not only useless but may actually be harmful.

Desoxycorticosterone, one of the crystalline cortical compounds which is most active in maintaining adrenalectomized animals, proved to have little if any effect even if large amounts were administered in divided doses. From this it may be concluded that some substance other than desoxycorticosterone is responsible for the high activity of the cortical extracts. In view of the fact that carbohydrate metabolism is seriously disturbed in shock and that corticosterone is much more active in influencing carbohydrate metabolism in cases of adrenal insufficiency than desoxycorticosterone it appears that the former might be responsible for the shock-combating effect of our cortical extract which contains both these compounds. Until corticosterone becomes commercially available active cortical extracts must be regarded as the most powerful hormonal agents which can be used for combating shock.

The expenses of this work have been defrayed through a grant received from the National Research Council of Canada. The authors take pleasure in expressing their gratitude to Professor C. P. Martin for his constant interest and encouragement, without which this work would probably never have been completed. Our thanks are also due to Dr. David Klein, of the Wilson Laboratories, for his generous supply of cortical extract and to Drs. G. Stragnell and E. Schwenk, of the Schering Corporation of Bloomfield, New Jersey, for the desoxycorticosterone acetate used in our experiments.

REFERENCES

1. SELYE, H.: *Brit. J. Exper. Pathol.*, 1936, 17: 234.
2. *Idem*: *Endocrinol.*, 1937, 21: 169.
3. LEBLOND, C. P.: *Ann. d'Endocrinol.*, 1939, 1: 179.
4. SELYE, H.: *Proc. Soc. Exp. Biol. & Med.*, 1938, 38: 728.
5. *Idem*: *Arch. Internat. Pharm. et Ther.*, 1937, 55: 431.
6. KARADY, S., BROWNE, J. S. L. AND SELYE, H.: *Quart. J. Exper. Physiol.*, 1938, 28: 23.
7. *Idem*: *J. of Biol. Chem.*, 1939, 131: 717.
8. MOON, V. H.: Oxford Medical Publications, 1938.
9. KELLAWAY, C. H. AND COWELL, S. J.: *J. of Physiol.*, 1922, 57: 82.
10. *Idem*: *J. of Physiol.*, 1922, 56: 20.
11. PERLA, D. AND MARMORSTON-GOTTESMAN, J.: *Am. J. Physiol.*, 1929, 89: 152.
12. *Idem*: *Proc. Soc. Exper. Biol. & Med.*, 1931, 28: 650.
13. WYMAN, L. C.: *Am. J. Physiol.*, 1928, 87: 29.
14. INGLE, D. J.: *Am. J. Physiol.*, 1937, 118: 57.
15. SELYE, H. AND SCHENKER, V.: *Proc. Soc. Exp. Biol. & Med.*, 1938, 39: 518.
16. WEIL, P. AND BROWNE, J. S. L.: *Science*, 1939, 90: 445.
17. *Idem*: *Proc. Canad. Physiol. Soc.*, Kingston, 1939.
18. HARTMAN, F. A. AND BROWNELL, K. A.: *Am. J. Physiol.*, 1931, 97: 530.
19. HARTMAN, F. A., GREENE, C. W., BOWEN, B. D. AND THORN, G. W.: *J. Am. M. Ass.*, 1932, 99: 1478.
20. HARTMAN, F. A.: *Ann. Int. Med.*, 1933, 7: 6.
21. DEMOLE, M. J.: *Rev. méd. Suisse Rom.*, 1932, 52: 402.
22. SCHITTTENHELM, A. AND BÜHLER, F.: *Zeitsch. f. Exper. Med.*, 1935, 95: 206.
23. VIALE, G.: *Monit. Endocrinol.*, 1933, 1: 27.
24. KOEHLER, A. A.: *Science*, 1931, p. 78.
25. BERMAN, L.: *Endocrinol.*, 1932, 16: 109.
26. POTTENGER, F. M.: *Endocrinol.*, 1937, 21: 449.
27. GRUBER, L.: *C. R. Soc. Biol.*, 1924, 91: 208.
28. LANGECKER, H. AND SINGER, E.: *Z. Immun. Forsch.*, 1933, 79: 326.
29. THOMPSON, J. T. AND WHITEHEAD, R. W.: *Endocrinol.*, 1931, 15: 495.
30. WHITEHEAD, R. W. AND SMITH, C.: *Proc. Soc. Exper. Biol. & Med.*, 1932, 29: 672.
31. ZWEMER, R. L. AND TRUSZKOWSKI, R.: *Science*, 1936, p. 558.
32. BAMBERGER, PH. AND WENDT, L.: *Klin. Wchnschr.*, 1935, p. 846.
33. PESCH, K. AND STRELOW, K.: *Biochem. Zeitsch.*, 1923, 140: 353.
34. EINHAUSER, M.: *Münch. med. Wchnschr.*, 1939, 86: 441.
35. WAGNER, B.: *Zbl. f. Gynäk.*, 1939, 63: 432.
36. MATTHEWS, H. B.: *J. Am. M. Ass.*, 1939, 113: 1183.
37. REED, F. R.: *Am. J. Surg.*, 1938, 40: 527.
38. RAGAN, C., FERREBEE, J. W. AND FISH, G. W.: *Proc. Soc. Exper. Biol. & Med.*, 1939, 42: 712.
39. SCUDDER, J.: Shock; Blood Studies as a Guide to Therapy, Lippencott, Phila., 1940.
40. PERLA, D., FREIMAN, D. C., SANDBERG, M. AND GREENBERG, S. S.: *Proc. Soc. Exper. Biol. & Med.*, 1940, 43: 397.
41. PARKINS, W. M., SWINGLE, W. W., TAYLOR, A. R. AND HAYS, H. W.: *Am. J. Physiol.*, 1938, 123: 668.
42. SELYE, H. AND DOSNE, C.: *Proc. Soc. Exper. Biol. & Med.*, 1939, 42: 580.
43. MADDALONI, F.: *Arch. ital. Med. sper.*, 1938, 2: 913.
44. WOLFRAM, J. AND ZWEMER, R. L.: *J. Exper. Med.*, 1935, 61: 9.
45. HEUER, G. J. AND ANDRUS, W. DE W.: *Ann. Surg.*, 1934, 100: 734.
46. FINE, J., FUCHS, F. AND MARK, J.: *Proc. Soc. Exper. Biol. and Med.*, 1940, 43: 514.
47. GIRAGOSSINTZ, G. AND SUNDSTROEM, E. S.: *Proc. Soc. Exper. Biol. & Med.*, 1937, 36: 432.
48. DESSAU, F.: *Acta brev. neerl. Physiol.*, 1935, 5: 173.
49. LASZT, L. AND VERZAR, F.: *Pflüger's Arch.*, 1936, 236: 693.
50. ZWEMER, R. L. AND TRUSZKOWSKI, R.: *Endocrinol.*, 1937, 21: 40.
51. SELYE, H. AND DOSNE, C.: *Am. J. Physiol.*, 1940, 128: 729.
52. FISHER, R. A.: Statistical Methods for Research Workers, 6th ed., Edinburgh, 1936, p. 128.
53. WEIL, P., ROSE, B. AND BROWNE, J. S. L.: *Proc. Soc. Biol. & Med.*, (in press). See also *Canad. M. Ass. J.*, 1940, 43: 8.

ADDENDUM

Since this communication went to press, Professor E. C. Kendall of the Mayo Clinic has kindly prepared corticosterone for us from 400 pounds of cattle adrenals generously donated by the Wilson Laboratories through the courtesy of Dr. David Klein. This enabled us to demonstrate beyond doubt that corticosterone is extremely active in combating traumatic shock. In one experiment in which shock was produced in the manner described above by intestinal manipulation, six rats (average body weight 160 g.) were treated with ten subcutaneous injections each of 0.2 mg. of corticosterone in 0.5 c.c. of distilled water, while similar controls received the same amount of distilled water only. One of the controls died while the others were killed thirty hours after the trauma together with the treated animals. The latter showed almost no decrease in body temperature and had an average blood volume of 3.3 c.c. (range: 2.8 to 3.8). This blood volume is quite normal for rats of this size. They were obviously in good condition. The controls showed a severe decrease in body temperature and a blood volume of only 2.1 c.c. on the average (range: 1.9 to 2.2). The difference in blood volume is highly significant ($P = 0.01$). This furnishes the final proof showing that for combating traumatic shock, corticosterone is the most active steroid so far examined.

THE REDUCTION OF MORTALITY FROM EXPERIMENTAL TRAUMATIC SHOCK WITH ADRENAL CORTICAL SUBSTANCES*

BY PAUL G. WEIL,† BRAM ROSE† AND J. S. L. BROWNE

Montreal

THE rôle of the adrenal cortex in the protective mechanism of the organism against damaging stimuli has been shown by many investigators. Swingle and Parkins[1] have shown that adrenalectomized dogs maintained in good health are extremely susceptible to trauma (testis, intestinal and muscle) and rapidly develop fatal shock after a degree of trauma that is negligible to a non-adrenalectomized dog. They have further shown that in the adrenalectomized dog pre-treated with large amounts of adrenal cortical extract shock did not develop after trauma to the testis. In the adrenalectomized dog treated with adrenal cortical extract after shock from intestinal manipulation and muscle trauma had developed recovery ensued, whereas spontaneous recovery following shock from such procedures had not been observed (Swingle *et al.*[2]). Zwemer and Jungeblut[3] observed an increased resistance of guinea pigs to diphtheria toxin after treatment with adrenal cortical extract. Adrenal cortical extract de-

* From the McGill University Clinic, Royal Victoria Hospital, Montreal, Canada.

The experiments reported here formed part of a thesis submitted by one of us (P.G.W.) to the Faculty of Graduate Studies and Research, McGill University, September, 1939. A report of this work was presented at the meeting of the Canadian Physiological Society, Kingston, November, 1939.

† Aided by a grant from the Banting Research Foundation.