

THE INFLUENCE OF THE ADRENAL GLANDS ON RESISTANCE.

II. THE TOXIC EFFECT OF KILLED BACTERIA IN ADRENALECTOMIZED RATS.

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In another paper the remarkable effect of pyogenic infections on the adrenal cortex is reviewed (1). The hypertrophy of the adrenal cortex found in chronic infections may reasonably be interpreted as due to an increased demand made upon the physiological function of that tissue. The characteristic lipoids in the cells of the cortex which are present even in complete fasting rapidly disappear in severe pyogenic infections as shown both by experimental studies and by human autopsy findings. These pathological changes suggest a participation on the part of the adrenal glands in the resistance to infection.

Several investigators have found an increased susceptibility of adrenal-insufficient animals for certain drugs (Lewis (2, 3); Boinet (4); Schwarz (5); Giusti (6); Scott (7)). Also the susceptibility to diphtheria toxin is increased in adrenal insufficiency (Lusena (8); Frisco (9); Oppenheim and Loeper (10); Lewis (3)). Lusena showed that rats, though naturally immune to diphtheria toxin, were susceptible to it after adrenalectomy. In spite of this interesting alteration in the defensive mechanism to certain toxic substances the literature offers few data on the influence exerted by adrenal function on the resistance to pyogenic infections, the usual causes of adrenal change in human pathology. Several early observers reported a slight increase in the resistance of animals to bacterial intoxication¹ after the removal of one adrenal (Langlois and Charrin (11); Oppen-

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¹ Here and throughout this paper the term bacterial intoxication is used to designate the harmful effect of bacterial substances, and is not to be understood as limited to the effect of soluble toxins.

heim (12); Lucibelli (13)). Obviously unilateral adrenalectomy as a method for producing adrenal insufficiency is unsatisfactory.

The only direct investigation of the resistance to pyogenic bacterial intoxication in adrenal insufficiency that we have found in the literature is by Frisco (9). Two adrenalectomized rabbits were susceptible to a dose of *Staphylococcus aureus* culture which produced no obvious effect in controls. One of the former was killed in 12 hours and the other developed an abscess in the ear. This author also claimed that the blood serum of the adrenalectomized rabbits had lost much of its bacteriolytic activity.

It is the purpose of the present paper to report a study of the resistance of adrenalectomized rats to bacterial intoxications.¹ By this method we hope to throw some new light on the involvement of adrenal function in the pyogenic process. In this study killed bacteria were used throughout in order to separate the factors of intoxication from those of invasion. The resistance of adrenalectomized rats to living organisms is now being investigated.

Methods.

Procedure.—The experiments were conducted upon the following plan. Rats were observed for several days under standard conditions and then operated upon.² Both adrenals were removed at the same time to produce adrenal insufficiency. The operative technique employed and the methods of caring for adrenalectomized rats have been previously described (7). A certain number of each group of rats were used as controls, and for this purpose one adrenal was usually removed. Other operations such as thyroidectomy and splenectomy served as control procedures in other cases.

At varying periods after operation the resistance of the rats to bacterial intoxication was tested. Streptococcus and staphylococcus were used, since they are the most important organisms in human pyogenic infections. The animals were injected intraperitoneally with killed bacteria, either in a single injection of a heavy suspension or in smaller amounts repeated daily. The doubly adrenalectomized rats when tested in this way had all recovered from the operation, were eating well, and could not be distinguished from the normal and operative control rats in adjoining cages.

RESULTS.

1. *Acute Intoxication.*—A heavy suspension of streptococcus was used to produce acute intoxication.

² All operations were performed under ether anesthesia.

The organism used was isolated from a human empyema case at the Massachusetts General Hospital. It was not hemolytic after prolonged cultivation on artificial media. The organisms (24 hour growth on chocolate agar) were suspended in saline and killed by heat. Two lots of the bacterial suspension were required, each of about 250 cc.; they were kept on ice in tubes containing about 10 cc. each. No chemical preservative was used. The first lot contained 35 billion streptococci per cc., the second 31 billion per cc. The first lot was made shortly after the isolation of the organism and the second lot 2½ months later from the same strain. No difference in the biological action of these two suspensions was observed, in either normal or adrenalectomized animals. The second suspension contained 32 mg. of nitrogen per 100 cc. (estimated protein 2 gm. per liter).

This suspension was injected intraperitoneally in normal and operative control rats. Ten singly adrenalectomized rats and five other operative control rats were tested, usually 1 week after operation. Each was given intraperitoneally an injection of from 3 to 5 cc. of the streptococcus suspension. Those that received 3 cc. showed no appreciable effect. 5 cc. caused mild symptoms. After the latter dose the rats became quiet, with fur ruffled for a few hours, but at no time did they fail to react normally to blowing or other mild stimulation. For 1 or 2 days they refused to eat. All of these control animals survived (Protocol 1).

Nineteen doubly adrenalectomized rats received 3 cc. of the same streptococcus suspension. The fact should be emphasized that at the time of injection (usually 1 week after operation) the adrenal-insufficient rats used in this experiment were indistinguishable from the control animals. The former had an average weight loss of 2.8 per cent, though three of them had gained in weight since operation. All of the doubly adrenalectomized rats were killed by the injection of 3 cc. of the streptococcus suspension; the maximum time of survival was 7 hours. Some of the rats were dead an hour and a half after the injection. The average survival was 4½ hours. Protocol 2 is a typical example of this effect.

Within half an hour after injection the adrenalectomized rats were usually showing symptoms that progressed in severity until death. The animals first became quiet with fur ruffled, then failed to react to mild stimulation. Finally coma ensued and frequently the rat had one or more convulsions shortly before exitus. Respiration

became gasping and stopped before cardiac failure. Thus, the same amount of the killed streptococci produced no symptoms in control rats and invariably caused death within a maximum of 7 hours in the doubly adrenalectomized rats.

Sixteen doubly adrenalectomized rats were injected intraperitoneally with 2 cc. of the streptococcus suspension. The result in every case was fatal. One of the animals survived for 36 hours, the others all died within 18 hours. Of nine doubly adrenalectomized rats injected with 1 cc., seven died within 24 hours, one died the following day, and one recovered after a marked reaction. Three rats were adrenalectomized in two stages and all three were killed by a dose of 2 or 3 cc. of the streptococcus suspension. In fact, no rat having at least one adrenal intact has been killed by this suspension of streptococcus in amounts up to 5 cc. (the largest dose employed), and no adrenalectomized rat has survived a dose of 2 or 3 cc.

Incidental factors do not seem to be responsible for this sharp distinction in susceptibility between adrenalectomized and adrenal-intact rats.

Evidence of this fact is found in the two following examples.

Rat 139 was thyroidectomized with the removal of at least part of the parathyroids. 9 days after operation the animal had lost 17 per cent of its weight and had a persistent diarrhea. In spite of the fact that it was obviously in poor condition it was injected intraperitoneally with 2 cc. of streptococcus suspension. After this the rat became quiet, but had fully recovered by the next morning. In contrast to the preceding case, Rat 220 was in excellent condition 14 days after double adrenalectomy, being active, eating well, and having no diarrhea. It had lost 7 per cent in weight. It was injected intraperitoneally with the same amount of the streptococcus suspension (2 cc.) and was dead within 4 hours (Protocols 3 and 4).

Having established the fact that a certain quantity of killed streptococci which produced scarcely appreciable symptoms in control animals invariably killed adrenalectomized rats, we endeavored to study the mechanism of this reaction.

2. *The Nature of the Toxic Substance.*—The bacterial suspension was separated into two parts, (a) the water-clear filtrate, and (b) the sediment. The latter was made up to the original volume again with saline, and adrenalectomized rats were injected intraperitoneally

with 4 cc. of each of these substances. The resuspended sediment proved fatal in the same acute manner as the original suspension, the rats dying within 6 hours, while the filtrate was usually without effect. From these experiments it would seem that the toxic substance is chiefly endocellular.

The sediment fraction contained 0.2 per cent protein, total nitrogen being calculated as protein nitrogen, while the filtrate gave scarcely any color on Nesslerization. This observation suggested the hypothesis that the susceptibility to bacterial intoxication might be a non-specific protein effect. Four rats were injected intraperitoneally with 3 cc. of 2.5 to 3 per cent solutions of egg albumin, containing twelve to fifteen times the amount of protein present in the streptococcus suspension. Three of these rats survived, and one died. In the latter case a complicating uterine infection was found.

The effect of globulin was not tried. It is impossible from the data at hand to define exactly the nature of the substance in the streptococcus suspension to which adrenalectomized rats are susceptible. It seems to be chiefly endocellular and the reaction does not appear to be entirely a non-specific protein effect.

3. *Chronic Intoxication.*—In order to study the reaction to a more chronic form of intoxication, adrenalectomized and operative control rats were injected daily with *Staphylococcus aureus* in much smaller amounts than in the preceding experiments. The organisms used were isolated from a case of furunculosis in the outpatient department of the Peter Bent Brigham Hospital. They were suspended in saline and killed by heat. No chemical preservative was used. 1 cc. represented 1 billion staphylococci.

Eighteen rats had survived their operation for over a month. They were together in two stock cages and had been kept in this way for at least 2 weeks. All were in good condition, and it was impossible to distinguish the doubly adrenalectomized from the singly adrenalectomized animals. Each rat was injected intraperitoneally daily with staphylococcus suspension. The amount used at first was 3 cc. This was increased to 5 cc. after four injections. Under this treatment individual rats died from time to time until nine were dead.

After receiving 62 cc. of the staphylococcus suspension apiece, nine of the original eighteen rats were surviving. No rat had died for the

TABLE I.
Chronic Staphylococcus Intoxication.

Date.	Description of rat.	Weight. gm.	No. of injections.*	Total suspension. cc.	Result.	Adrenals.	Remarks.
1923							
Apr. 26	Tan; female.	250	1	3	Died.	Both out.	Thyroid large; gastric ulcer; hydrothorax.
" 30	" male.	240	5	17	"	"	Hydrothorax; thyroid large; gastric ulcer.
May 1	White "	350	6	22	"	"	Echinococcus pneumonia.
" 2	" "	300	6	22	"	"	Gastric ulcer.
" 5	" and tan; male.	220	9	37	"	"	
" 5	" male.	175	9	37	"	"	
" 7	" "	210	11	47	"	"	
" 8	Tan "	255	12	52	"	"	
" 9	" female.	120	14	62	"	"	
May 14	White female.	205	16	77	Survival.	Both intact.	Early pregnancy.
" 14	" and tan; female.	305	16	77	"	Left "	
" 14	" male.	305	16	77	"	" "	
" 14	" "	250	16	77	"	" "	
" 14	Tan "	195	16	77	"	" "	Echinococcus pneumonia; abscess in scrotum.
" 14	White; female.	175	16	77	"	Both "	Thyroidectomized; diarrhea.
" 14	" male.	340	16	77	"	Left "	Echinococcus cysts in mesentery.
" 14	" "	350	16	77	"	" "	" pneumonia.
" 14	" "	350	16	77	"	" "	

* Injection of *Staphylococcus aureus* (killed) suspension (1 billion per cc.). Started April 25, 1923. All surviving rats sacrificed with ether on May 14, 1923.

past 3 days and all of them seemed to be in good condition. Each of these surviving animals was given intraperitoneally 10 cc. of the bacterial suspension, which they all withstood without symptoms. 2 days after this final injection the surviving nine animals were sacrificed with ether. Every rat that died as the result of staphylococcus intoxication had had both adrenals removed. All of the animals that survived had at least one adrenal intact (Table I).

Cortex versus Medulla.

As shown in this study, the removal of both adrenals invariably leads to a remarkable decrease in the resistance of rats to bacterial intoxications. This is presumably a consequence of the loss of some function of the cortex or of the medulla, as the control operations in which this result is never seen include all the other factors of the operation, as for example traumatization of the structures in the neighborhood of one adrenal combined with the removal of the other. It seemed unlikely that the increased susceptibility of adrenalectomized rats was in any way related to epinephrine secretion. This point, however, was tested experimentally.

It appeared impossible to separate the functions of the two parts of the gland in rats by removing the medulla as Wislocki and Crowe (14) and Houssay and Lewis (15) had done in dogs. However, one adrenal was removed and the other denervated. Rats prepared in this way were injected with 3 cc. of the streptococcus suspension. They reacted like the control animals and survived this dose, which is invariably fatal to doubly adrenalectomized rats (Protocol 5). Stewart and Rogoff (16) have shown that after section of the splanchnic nerves the secretion of epinephrine is immeasurably small so it seems probable that the lack of epinephrine secretion in the adrenalectomized rats plays no part in their increased susceptibility to bacterial intoxications. The data presented do not completely rule out the possibility that the adrenal medulla, separated from its nervous connections, may react locally with the toxic substance. However, indirect evidence indicates that the increased susceptibility to bacterial or drug intoxication is related to cortical function. Thus there seems to be a parallelism in time after adrenalectomy between the recovery

of a normal resistance to morphine and the hypertrophy of accessory adrenal rests consisting solely of cortical cells (3, 7). In Lusena's experiments (8) the presence of a small amount of cortical tissue sufficed to save the adrenalectomized rats from the otherwise fatal effect of diphtheria toxin. The susceptibility of adrenalectomized rats to bacterial intoxication seems to be due to the loss of some cortical function and not to be related to a lack of epinephrine secretion.

Attempts at Protection.

Changes in the adrenal cortex caused by acute infection and especially the disappearance of its characteristic lipoids, together with its marked hypertrophy in chronic infections, seem to indicate a relative insufficiency of adrenal cortical function in pyogenic conditions. On account of its possible clinical application to human infections, then, the protection of adrenal-insufficient animals against bacterial intoxication is an important problem. The convulsions caused by the bacterial intoxication in adrenalectomized rats frequently had a prominent feature; *viz.*, a peculiar rolling character. They resemble strikingly those seen in insulin-treated rabbits. This fact suggested that the fatal effect of the bacterial injection in adrenalectomized rats might be due to hypoglycemia. However, glucose given intravenously or intraperitoneally had no protective action.

The disappearance of lipoids from the adrenal cortex naturally attracts attention to this group of substances. It is easy enough to demonstrate typical anisotropic fluid crystals in extracts of the ox adrenal. The reintroduction of the extracted lipoids in an absorbable, non-toxic form is a technical problem of great magnitude. As yet, this method, which still seems promising, has not given any conclusive results. In spite of repeated efforts, no substance has as yet been found to protect adrenalectomized rats against bacterial intoxication.

DISCUSSION.

1. The Adrenal Glands and Resistance to Bacterial Intoxication.

An interesting relationship between the adrenal cortex and the infectious process has been suspected from (1) the constancy of

adrenal lesions in acute infections, (2) the disappearance of the characteristic lipoids in acute infections, and (3) the hypertrophy of the adrenal cortex in chronic pyogenic processes. No conclusive proof, however, that the adrenal glands played any part in the resistance to intoxication by pyogenic organisms has heretofore been offered. By selecting the proper dosage of organisms, as was done in the present work, adrenal-insufficient rats can be invariably killed by a bacterial intoxication, which adrenal-intact animals always survive. Whether the cortical accessories can in time hypertrophy sufficiently to protect against bacterial intoxications as completely as the original glands has not been determined. At least 6 weeks after adrenalectomy, however, adrenalectomized rats are still susceptible to repeated injections of killed staphylococci which are harmless to control animals.

2. Protective Function of the Adrenal Cortex.

The susceptibility of adrenalectomized rats to bacterial intoxication apparently furnishes evidence of an important function of the adrenal cortex. It has long been established that this tissue seems to be essential to vertebrate life (Biedl (17)). In addition to this fact almost nothing has been known about its functions until very recently. The effect of adrenal insufficiency on heat production seems likewise to be dependent on the adrenal cortex (Marine and Baumann (18); Scott (19)). The diminished resistance of adrenalectomized rats to various drugs as reported by Lewis (3), and corroborated in the case of morphine by Scott (7), appears by analogy to be probably due also to insufficiency of the cortex alone, though this point has not been directly tested. In our experiments a denervated adrenal served to maintain the resistance of the rat to bacterial intoxication in the same manner as a gland with intact medullary secretion, while the removal of the whole adrenal profoundly affected the susceptibility of rats to bacterial intoxication. The available evidence indicates, then, that resistance to bacterial intoxication is dependent upon a function of the adrenal cortex.

The susceptibility of an organism to infection is controlled by (1) the virulence of the invading organism, and (2) the resistance of the animal. With a given infection, the outcome will depend on the

resistance of the animal. The science of immunology has taught us concerning one type of resistance; *viz.*, specific antibodies. The non-specific elements in the resistance to bacterial infections and intoxications are also generally considered important, but little is known about their nature. The functional condition of the adrenal cortex seems to be an essential element in a non-specific resistance to the harmful effects of bacterial intoxications. Indeed, the reaction involved in the formation of specific antibodies may possibly impose a functional demand upon the adrenal cortex. Porak (20) states that the repeated immunization of animals in the Wassermann laboratory at Paris produced the most marked hypertrophy of the adrenal cortex that he had seen. Certainly the functional status of the adrenal cortex must be considered in future studies of resistance to infection or bacterial intoxication.

3. *Detoxification or Metabolic Effect.*

The early literature on adrenal function advanced the interesting but unsupported hypothesis that these glands possessed a detoxifying power in the sense that some reaction occurred between the toxic substance and an adrenal product (Oppenheim (21)). The circumstantial evidence presented to support this theory is inconclusive, and much of it has been discredited (Tawara (22); Exner (23)). That the protective function of the adrenal glands is due to a detoxication, in accordance with this hypothesis, seems unlikely. The alternative explanation that the susceptibility of adrenalectomized animals is due to a fundamental metabolic effect of the adrenal insufficiency appears to correspond more closely to the type of reaction observed. By using very small doses of bacteria, the same profound, prolonged disturbance in the condition of the adrenalectomized rat can be produced that was noted previously as an effect of morphine. Such animals ate little and showed a greatly diminished activity, finally dying after a number of days. The susceptibility of an adrenal-insufficient animal to bacterial intoxication seems to be dependent on some function of the adrenal cortex. Whether the state is consequent on a lack of detoxification by the adrenal cortex, or comes about indirectly through the effect of adrenal insufficiency on some other tissue is being investigated.

4. *Extreme Susceptibility of a Small Group.*

A few doubly adrenalectomized rats chiefly belonging in the group of 10 per cent that have a severe reaction to adrenalectomy, yet survive 2 weeks or more, exhibit a greatly reduced resistance to substances that are not toxic to most adrenalectomized animals. Examples of this extreme sensitivity are afforded by the rat killed by the intraperitoneal injection of egg albumin, and the one in which the clear filtrate from the streptococcus suspension produced an intoxication fatal after 4 days. Because of such instances the minimum lethal dose is an unsatisfactory standard whereby to judge the susceptibility of adrenalectomized rats. The diminished resistance to bacterial intoxication is not an unusual reaction of the sort mentioned, for every adrenalectomized rat shows it.

5. *Exhaustion of Adrenal Accessory Lipoids.*

No systematic study of the histological appearance of the accessory cortical rests was made. However, a marked difference was observed between the cortical accessory cells of adrenalectomized rats (1) that were sacrificed, and (2) that were killed by a chronic bacterial intoxication. In the former the cells showed the typical honeycombed appearance (hematoxylin and eosin preparations) signifying abundant lipoid granules, while in the latter the cells were shrunken, pycnotic, and not honeycombed. This is the same type of change seen in the adrenal cortex in pyogenic infections, and it furnishes further evidence in correlation of the results of bacterial intoxication with the disappearance of lipoids from the adrenal cortical cells. This again raises the important question whether the lipoid granules are the precursors of an internal secretory product of the adrenal cortex, or possibly the menstruum of the active principle. No direct proof of such a secretion has been brought. Yet the evidence of Dietrich (24) is highly suggestive of it. He observed diminution in size and peripheral (juxtavascular) arrangement in the cell of the lipoid granules as the first stage of lipoid disappearance accompanying infected war wounds. Fatal wounds unaccompanied by infection were invariably associated with a large amount and uniform distribution of lipoid granules in the cell.

CONCLUSION.

1. The resistance of rats to bacterial intoxication is greatly decreased after double adrenalectomy.

2. This decreased resistance is dependent upon a functional insufficiency of the adrenal cortex.

3. A dose of killed streptococci or staphylococci can be obtained that is invariably fatal to adrenalectomized rats, before hypertrophy of cortical accessories, but never kills control rats.

I wish to acknowledge my indebtedness to Dr. David Marine who first suggested to me the importance of the adrenal cortex in the defensive mechanism against harmful biological processes, and also to express my appreciation to Dr. A. W. Sellards and Dr. W. B. Cannon for advice in this investigation.

Control.

Protocol 1.—Rat 70. White, female.

Nov. 24, 1922. Individual cage. Active.

Nov. 27. Active, eating well, weight 197 gm. Operation: excision of right adrenal. Easy operation. Moderate fat.

Dec. 4. Active, eating well, weight 195 gm. At 11 a.m. injected 5 cc. of streptococcus suspension (35 billion per cc.) intraperitoneally. Became somewhat quiet, but reacted vigorously to blowing. 5 p.m. Fairly active, fur slightly ruffled.

Dec. 5. Active, but not eating.

Dec. 7. Active, beginning to eat. Weight 179 gm.

Jan. 8, 1923. Active, weight 217 gm.

Adrenal Insufficiency.

Protocol 2.—Rat 87. Tan and white, male.

Dec. 6, 1922. Individual cage.

Dec. 11. Active, eating well. Operation: excision of both adrenals.

Dec. 18. Active, eating well, weight 340 gm. At 10.30 a.m. injected 3 cc. of streptococcus suspension (35 billion per cc.) intraperitoneally. 1.30 p.m. Semicomatose. Dead at 2 p.m.

Autopsy.—Thyroid large and red. Heart and lungs normal. Abdomen: about 2 cc. of free fluid. Adrenals absent. No accessories seen. Much retroperitoneal fat. Stomach: mucous membrane smooth.

Control (Thyroidectomy).

Protocol 3.—Rat 139. White, female.

Feb. 10, 1923. Active, weight 187 gm. Operation: thyroidectomy and partial parathyroidectomy. Severe hemorrhage.

Feb. 12. Rather quiet. Diarrhea. Not eating well.

Feb. 19. Diarrhea has been persistent since operation. Quiet. Evident loss of weight. Muscle tone poor. Weight 155 gm. At 11.30 a.m. injected 2 cc. of streptococcus suspension (31 billion per cc.) intraperitoneally. At 5.30 p.m. quiet. Reacts briskly to blowing. Diarrhea. 9 p.m. alert.

Feb. 20. Quiet but alert. Diarrhea. Ate nothing yesterday.

Feb. 21. Fairly active. Eating well. Diarrhea unchanged.

Apr. 5. In good condition.

Adrenal Insufficiency.

Protocol 4.—Rat 220. White, female.

Apr. 17, 1923. Active, weight 165 gm. Operation: double adrenalectomy. Easy operation.

May 1. Active, eating well, weight 153 gm. At 1.06 p.m. injected 2 cc. of streptococcus suspension (31 billion per cc.). 2.30 p.m. Quiet. Found dead at 5 p.m.

Autopsy.—Thyroid: moderate size. Heart and lungs normal. Abdomen: adrenals out. Right kidney adherent to the liver. Much retroperitoneal fat. Stomach: congestion of mucous membrane. No ulcers.

Denervation of Adrenal.

Protocol 5.—Rat 237. White, female.

Apr. 28, 1923. Active, weight 218 gm. Operation: excision of right adrenal; denervation of left adrenal.

May 3. Active, weight 210 gm. At 12 noon injected 3 cc. of streptococcus suspension (31 billion per cc.) intraperitoneally. No symptoms noted during the afternoon.

June 1. Active, eating well.

BIBLIOGRAPHY.

1. Scott, W. J. M., and Davidson, P. B., Adrenal lipoids in pathological conditions (unpublished data; reported in abstract: Scott, W. J. M., *J. Med. Research*, 1923, xliv, 109).
2. Lewis, J. T., Sensibilité des rats privés de surrénales envers les toxiques, *Compt. rend. Soc. biol.*, 1921, lxxxiv, 163.
3. Lewis, J. T., Sensibility to intoxication in albino rats after double adrenalectomy, *Am. J. Physiol.*, 1923, lxiv, 506.

4. Boinet, E., Diminution de résistance des rats doublement décapsulés à l'action toxique de diverses substances, *Compt. rend. Soc. biol.*, 1897, xlix, 466.
5. Schwarz, O., Über Stoffwechselstörungen nach der Extirpation beider Nebennieren, *Arch. ges. Physiol.*, 1910, cxxxiv, 259.
6. Giusti, L., Sensibilità aux toxiques des Crapauds acapsulés ou sans hypophyse, *Compt. rend. Soc. biol.*, 1921, lxxxv, 312.
7. Scott, W. J. M., The influence of the adrenal glands on resistance. I. The susceptibility of adrenalectomized rats to morphine, *J. Exp. Med.*, 1923, xxxviii, 543.
8. Lusena, G., La resistenza alle intossicazioni batteriche dopo l'estirpazione delle capsule surrenali, *Boll. r. Accad. med. Genova*, 1903, xviii, 29.
9. Frisco, B., Le capsule surrenali nei loro rapporti col ricambio materiale e coll'immunità naturale dell'organismo, *Gior. internaz. sc. med.*, 1897, xix, n.s., 241.
10. Oppenheim, R., and Loeper, M., L'insuffisance surrénale expérimentale par lésions directes des capsules, *Compt. rend. Soc. biol.*, 1903, lv, 332.
11. Langlois and Charrin, Du rôle des capsules surrénales dans la résistance à certaines infections, *Compt. rend. Soc. biol.*, 1896, xlvi, 708.
12. Oppenheim, R., Rôle des capsules surrénales dans la résistance à la toxiféction diphtérique, *Compt. rend. Soc. biol.*, 1901, liii, 316.
13. Lucibelli, G., Contributo alla fisiopatologia delle capsule surrenale, *Gazz. osp.*, 1901, xxii, 1221.
14. Wislocki, G. B., and Crowe, S. J., Note on the abdominal chromaffin body in dogs, *Bull. Johns Hopkins Hosp.*, 1922, xxxiii, 377; also personal communication.
15. Houssay, B. A., and Lewis, J. T., The relative importance to life of cortex and medulla of the adrenal glands, *Am. J. Physiol.*, 1923, lxiv, 512.
16. Stewart, G. N., and Rogoff, J. M., Quantitative experiments on the liberation of epinephrin from the adrenals after section of their nerves, with special reference to the question of the indispensability of epinephrin for the organism, *J. Pharmacol. and Exp. Therap.*, 1917-18, x, 1.
17. Biedl, A., Innere sekretion. Ihre physiologischen Grundlagen und ihre Bedeutung für die Pathologie, Berlin and Vienna, 2nd edition, 1913.
18. Marine, D., and Baumann, E. J., Influence of glands with internal secretion on the respiratory exchange. II. Effect of suprarenal insufficiency (by removal or by freezing) in rabbits, *Am. J. Physiol.*, 1921, lvii, 135.
19. Scott, W. J. M., Influence of glands with internal secretion on the respiratory exchange. IV. Effect of suprarenal insufficiency in cats, *J. Exp. Med.*, 1922, xxxvi, 199.
20. Porak, R., L'hypertrophie et la teneur en adrénaline des surrénales dans les infections, les intoxications, et certains états d'immunité, *J. physiol. et path. gén.*, 1919-20, xviii, 95.

21. Oppenheim, R., *La fonction antitoxique des capsules surrénales*, Thèse de Paris, Paris, 1902.
22. Tawara, S., *Du mode d'action de l'adrénaline et des acides vis-à-vis des toxines bactériennes*, *Compt. rend. Soc. biol.*, 1921, lxxxv, 401.
23. Exner, A., *Über die durch intraperitoneale Adrenalininjektion verursachte Verzögerung der Resorption von in den Magen eingeführten Giften*, *Arch. exp. Path. u. Pharmacol.*, 1903, 1, 313.
24. Dietrich, A., *Die Nebennieren bei den Wundinfektionskrankheiten*, *Centr. allg. Path. u. path. Anat.*, 1918, xxix, 169.