

from behind. If you will do that in every case you won't miss any of these cases of osteochondritis dissecans that were mentioned in the author's paper. About preoperative exercises, I think it is important to tell the patient who is going to have an operation on his knee that he must practice using his quadriceps before the operation. There was a time when I used to give patients a typewritten slip saying "You must practice exercising your quadriceps before the operation because as soon as you wake up from the anesthesia (if it is a general anesthetic) I am going to insist that you raise your heel off the bed regardless of how much or how little pain it causes you." I tell them to tighten the knee, point the toes and raise the heel off the bed. They can do it with only one muscle and that is the quadriceps. If they are used to it before the operation and are thinking about it when going under the anesthetic, it is easy to get them to do it afterward. Postoperatively, they must elevate it whether they have a cast on or not, and if one has a compression cast on, they elevate that straight leg easier than if they have a pressure bandage on.

DR. HAROLD R. BOHLMAN, Baltimore: With regard to Dr. Smith's comment on air embolus, we feel pretty safe in this field. In none of these cases have we had embolism occur, even when we put in air immediately after operating, before we put on the dressings. The human body will tolerate a certain amount of intravenous air. Firor some years ago demonstrated that a dog could tolerate from 18 to 25 cc. of air in his venous system without great difficulty. I have had two cases of air embolism occur in gonorrheal arthritis joints, one of which I tried to distend when adhesions were present and another in which the joint space had been partially obliterated and I used too much tension. The immediate results were startling and very embarrassing to the patient and to the doctor as well, but neither resulted in a fatality. A number of these have been reported in the literature. I once suffered one bit of experience with air emboli in my veins while giving blood for a transfusion and somebody hooked up the vacuum pump in reverse. It was startling to feel the air gurgling up my brachial vessels; it raised my blood pressure and pulse rapidly but did no harm, although it gave me a bad start for a little while. With regard to Dr. Lewin's question on the acusector, that may not be a good term. I have forgotten who used it first, but I use it in association with a small knifelike instrument which has an insulated handle and is hooked up to a machine with a current of radio frequency characteristics. I refer to the Burdick machine, which I believe has a blended spark gap and tube current; for information on this, I refer you to Ward and Kelly's book on electro-surgery, which was published some eight years ago. Quadriceps atrophy I think depends a good deal on the duration of the disability before operation. In the oldest case in this series there were symptoms of twenty-five years' standing. The internal semilunar cartilage was badly chewed up and distributed about the joint, many pieces attached to the synovial membrane, as Timbrel Fisher notes loose bodies often do. This patient had a great deal of atrophy of the quadriceps muscle, but it came back surprisingly fast after a quarter of a century of disability of that knee. It was amazing to see how rapidly, without any particular help on our part, the quadriceps developed form and function.

Vitamin C.—Most animals do not get scurvy, however badly they are fed. They can make their own vitamin C, as the anti-scurvy factor is called. But monkeys and guinea pigs need it like men. And when Holst and Frölich produced scurvy in guinea pigs in Norway in 1907 it soon appeared that it was due to lack of a substance needed in small amounts; and the quantities in different foods could be roughly measured in doses needed to cure a guinea pig. I was in the next room when Szent-Györgyi, a Hungarian working at Cambridge, isolated vitamin C. He was not looking for it and did not know that his crystals were the vitamin. He had tracked down and purified a substance found in various plants and concerned in oxidations inside the cells of both plants and animals, where it plays a part somewhat like that of hemoglobin in the animal body as a whole.—Haldane, J. B. S.: Science and Everyday Life, New York, Macmillan Company, 1940.

COMPENSATORY ATROPHY OF THE ADRENALS

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It is well known that following partial removal of an endocrine gland the remaining parts of the organ tend to compensate for the loss by undergoing active hypertrophy and hyperplasia. This phenomenon has been referred to descriptively as compensatory hypertrophy. The isolation of purified hormone principles made it possible to study the effect of hormone overdosage on endocrine glands, and it soon became evident that in most cases excessive treatment with a certain glandular substance resulted in the eventual atrophy of the cells which normally have the task of producing this glandular product. It is not within the scope of this com-

TABLE 1.—*The Action of Desoxycorticosterone Acetate on Adrenal Weights in the Rat*

Material Injected	Number of Rats	Sex	Length of Treatment, Days	Body Weight, Gm.	Adrenal Weight, Mg.	Significance of Adrenal Weight Change *
Oil.....	6	♂	10	152	39	Control
Desoxycorticosterone acetate.....	6	♂	10	152	20	P = <0.01
Cholesterol.....	6	♂	20	150	40	Control
Desoxycorticosterone acetate.....	6	♂	20	150	20	P = <0.01
Normal not injected.....	6	♂	20	159	38	Control
Normal not injected.....	6	♀	20	116	53	Control
Cholesterol.....	12	♂	20	157	39	P = 0.5
Cholesterol.....	12	♀	20	117	44	P = 0.1
Desoxycorticosterone.....	6	♂	20	159	19	P = <0.01
Desoxycorticosterone.....	6	♀	20	122	22	P = <0.01
Pregnandiol.....	5	♂	20	165	38	P = 0.8
Pregnandiol.....	5	♀	20	124	49	P = 0.3
Δ ⁵ -dehydro-iso-androsterone.....	5	♂	20	169	36	P = 0.2
Δ ⁵ -dehydro-iso-androsterone.....	5	♀	20	124	38	P = 0.01
Δ ⁵ -pregnenol-3-one-20.....	5	♂	20	160	34	P = 0.4
Δ ⁵ -pregnenol-3-one-20.....	5	♀	20	124	52	P = 0.1

* In all experiments reported in this paper, the significance of the apparent differences between the treated and control series was evaluated by "Student's" method for small samples (Fisher, R. A.: Statistical Methods for Research Workers, ed. 5, London, Oliver & Boyd, 1938, p. 128) and is expressed in terms of probability, estimated by graphic interpolation in Fisher's table of t. In accordance with the usual convention, differences between series cannot be accepted as significant when P is greater than 0.05. In each series the untreated animals or, in case all animals were injected, only the groups receiving oil or cholesterol were used as controls, since treatment with the latter substances proved ineffective in causing a change in the adrenal weight.

munication to review the extensive relevant literature. Suffice it to mention that the thyroid gland undergoes involution under the influence of an overdose of a thyroid preparation,¹ the pancreatic islets, especially the insulin producing beta cells, involute following treatment with insulin,² the ovaries after administration of estrogen³ or progesterone,⁴ the testis after androgen

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Owing to lack of space, this article has been abbreviated by omission of some of the illustrations. The complete article appears in the author's reprints.

Read before the Section on Pathology and Physiology at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

The expenses of this work have been defrayed through a grant received from the Schering Corporation of Bloomfield, N. J. Drs. Gregory Stragnell and E. Schwenk of this corporation supplied all the steroids used in this work except the pregnandiol, which was donated by Ayerst, McKenna and Harrison through the courtesy of Dr. Stanley Cook. The photomicrographs have been prepared by Mr. K. Nielsen and the microscopic slides by Mr. C. Rasmussen.

1. Loeb, Leo; Bassett, R. B., and Friedman, H.: Proc. Soc. Exper. Biol. & Med. **28**: 209 (Dec.) 1930.

2. Muggia, Aldo: Arch. per le sc. med. **50**: 185, 1927. Miyari, S.: Mitt. d. med. Gesellsch. zu Tokyo, 1928, vol. 42, No. 7.

3. del Castillo, E. B., and Calatrava, C. J.: Rev. Soc. argent. de biol. **6**: 108, 1930. d'Amour, F. E.: J. Biol. Chem. **92**: lxxxv (June) 1931.

4. Selye, Hans; Browne, J. S. L.; and Collip, J. B.: Proc. Soc. Exper. Biol. & Med. **34**: 472 (March) 1936.

therapy,⁵ the parathyroids after administration of solution of parathyroid⁶ and the adrenal cortex after administration of adrenal cortex extract⁷ or desoxycorticosterone.⁸ Even the pituitary shows degenerative changes in animals chronically treated with hypophysial extracts.⁹ It appears logical to refer to this atrophy as "compensatory atrophy," since it is the exact antithesis of compensatory hypertrophy and appears to be the result of a readjustment of endogenous hormone production in an organism which is flooded with an exogenously introduced glandular preparation. In the case of the endocrine glands which stand under the regulating influence of the pituitary, it is most probable that compensatory atrophy is due to a decrease in the elaboration of the corresponding tropic hormone. This is shown by the fact that estrogens cause no atrophy in hypophysectomized animals whose ovaries are maintained by daily injections of gonadotrophic substance,¹⁰ and cortical preparations fail to cause cortical atrophy in intact rats receiving adrenotropic substance by injection.¹¹

If the phenomenon of compensatory atrophy, as defined, is considered from the point of view of its clinical significance, it is evident that it could never serve to inhibit an excess production of hormone by an endocrine organ since, in order to produce atrophy of an overfunctional gland, one would have to administer a further excess of the same endocrine substance which is already present in unusually large amounts in the circulation of the patient. In such cases the possible benefit which could be derived from the inhibitory action exerted by the hormone on the overactive gland is outweighed by the damage which would be produced by aggravating the existing endocrine overdosage. Yet the endocrine treatment of diseases of hormone oversecretion would appear to be of the greatest clinical significance, since, in spite of all the progress made in the substitution therapy for hormone deficiencies, elimination of the hyperactive gland by surgical means or roentgen therapy are still the only reliable methods of coping with diseases of excess production of hormone.

In view of these considerations, an effort was made to determine whether treatment with glandular substances chemically similar to but physiologically different from those produced by a gland of internal secretion could also result in its compensatory atrophy. It was felt that if this should be the case it might open new methods of therapy, because the direct peripheral effects of the introduced substance would be different from those of the hormone elaborated by the hyperactive gland and would not necessarily aggravate the existing condition of overproduction of hormone.

5. Korenchevsky, V.; Dennison, M., and Kohn-Speyer, A.: Biochem. J. **27**: 557, 1933. Schoeller, W., and Gehrke, M.: Biochem. Ztschr. **264**: 352, 1933.

6. McJunkin, F. A.; Tweedy, W. R., and Breuhaus, H. C.: Parathyroid Hormone: Its Regulatory Action on Parathyroid Glands and Toxic Effect on Tissues of Rat, Arch. Path. **14**: 649 (Nov.) 1932.

7. Ingle, D. J., and Kendall, E. C.: Science **86**: 245 (Sept. 10) 1937.

8. Selye, Hans: Canad. M. A. J. **42**: 113 (Feb.) 1940.

9. Collip, J. B.; Selye, Hans, and Thomson, D. L.: Proc. Soc. Exper. Biol. & Med. **31**: 682 (March) 1934.

10. Selye, Hans, and Collip, J. B.: Endocrinology **20**: 667 (Sept.) 1936.

11. Ingle, D. J.; Higgins, G. M., and Kendall, E. C.: Anat. Rec. **71**: 363 (July 25) 1938. Ingle and Kendall.⁷

The discovery that either estrogenic or androgenic substances may cause gonadal atrophy in both sexes,¹² which fact was confirmed with crystalline synthetic androgens and estrogens,⁸ was an encouraging indication that at least in certain cases such a "transferred compensatory atrophy" is possible. However, in this instance the resulting atrophy is most probably due to the inhibition of gonadotrophic hormone production, and since the latter is responsible for the maintenance of both ovary and testis it appeared possible that we are dealing with a rather unique example. Yet in cases of excessive estrogen production (e. g. women in the menopause), inhibition of ovarian function by androgens or progesterone (which, as was said, also causes ovarian atrophy) may prove of therapeutic significance. Another observation that may perhaps be interpreted as an example of transferred compensatory atrophy is the observation of de Fremery,¹³ who found that diiodotyrosine causes the normally active thyroid glands of immature rats to assume the resting type. The fact that this inhibition is not due to a direct action on the thyroid is well shown by the fact that the "resting" thyroids of rats treated with diiodotyrosine remain so sensitive to exogenously introduced thyrotropic preparations that the author recommended animals so treated

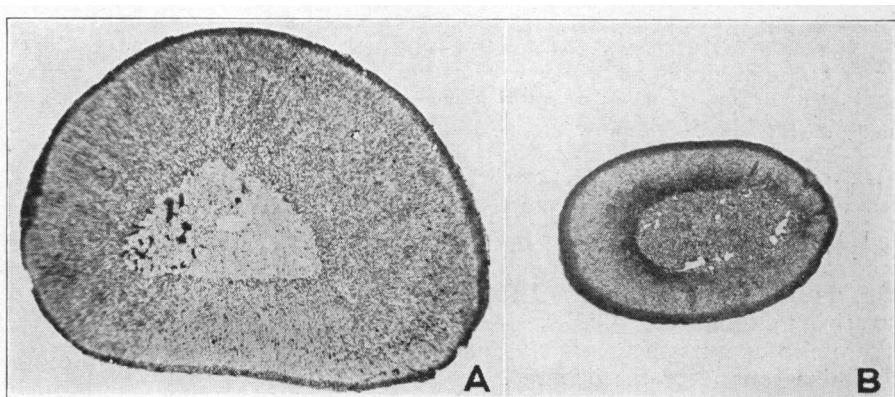


Fig. 1.—A, low magnification of cross section through adrenal of normal control female rat. B, low magnification of cross section through adrenal of female rat treated with desoxycorticosterone acetate. Note marked involution of the cortex while the medulla is but slightly subnormal in size.

to be used for the bio-assay of thyrotropic extracts. It appears quite possible that the diiodotyrosine molecule, which differs but slightly from that of thyroxine, retains the latter's ability to cause compensatory thyroid atrophy though it loses its other physiologic actions.

In the present communication I report a series of experiments in which the compensatory atrophy of the adrenals was submitted to a systematic study. This appeared especially interesting since the adrenal produces a large number of hormone principles, many of which are available in pure crystalline form. It was thought, therefore, that this gland would furnish an excellent test object on which to study the question of whether overdosage with one hormone principle made by a certain cell could inactivate this cell sufficiently to prevent it from producing not only this but also the other hormones which it usually elaborates.

THE ACTION OF DESOXYCORTICOSTERONE

Among the investigators who studied the action of life-preserving adrenal cortex extracts on the adrenals, some claimed that these produce no significant change¹⁴

12. Moore, C. R., and Price, Dorothy: Am. J. Anat. **50**: 13 (March) 1932.

13. de Fremery, P.: Acta brev. Neerland. **5**: 35, 1935.

14. Lippross, O.: Endokrinologie **18**: 18, 1936. King, J. L.: Proc. Soc. Exper. Biol. & Med. **35**: 619 (Jan.) 1937.

while others observed definite involution of the cortex without any lesion in the medulla.¹⁵ With regard to the isolated cortical steroids, Ingle and his associates¹¹ and Kendall¹⁶ showed that crystalline dehydrocorticosterone and corticosterone are extremely active in causing involution of the adrenal cortex of the rat when given in daily doses of 3.3 mg. The latter investigator claimed, however, that desoxycorticosterone and its acetate differ

which may perhaps be ascribed to the proportionately larger cortex in this sex.

Numerous investigators have studied the action of cortical steroids on the "X zone" of the mouse adrenal, which, in the opinion of some, represents the "androgenic" or male hormone secreting part of the cortex. This zone is well developed in prepuberal animals of both sexes but disappears in the male after sexual

maturity is attained and reappears only in case of castration. The question of whether the life-maintaining cortical principles influence this zone as well as the rest of the cortex is of especial interest, because functionally the X zone supposedly differs from the remaining cortical tissue. Robson and Taylor²¹ asserted that cortex extracts containing the life-maintaining principle elicit no change in the adrenals of the mouse. Howard²² obtained similar negative results with desoxycorticosterone and from this she concluded that the disappearance of this zone is specific to androgens, so that one may regard it as functionally not equivalent to the permanent cortex of the

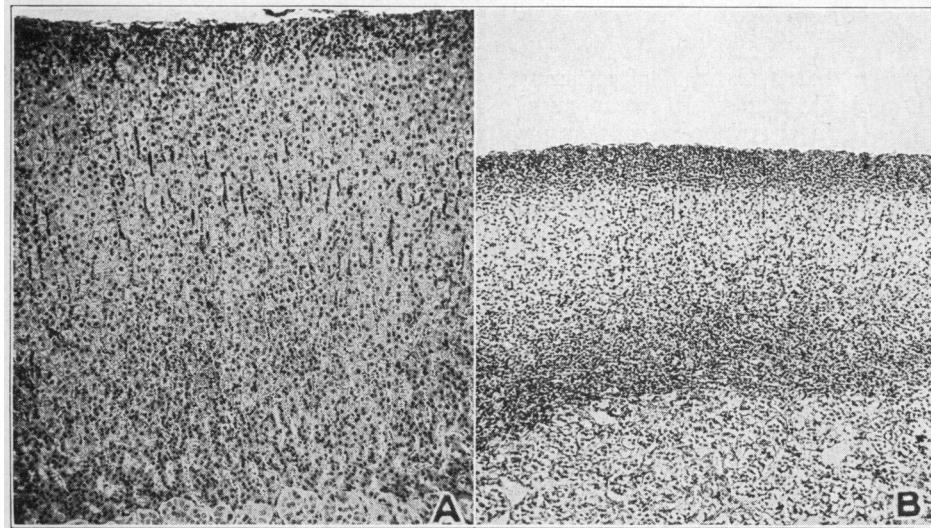


Fig. 2.—A, high magnification through total width of adrenal cortex of normal female rat. B, adrenal cortex of female rat treated with desoxycorticosterone acetate at same magnification as in A. Note marked atrophy of entire cortex without predilection for any particular zone.

from the aforementioned compounds in that they do not cause significant atrophy. On the other hand, Dosne and I¹⁷ showed that slight cortical atrophy may be produced by comparatively small doses (2 mg. a day) of this compound, and larger quantities (10 mg. a day) invariably elicit severe atrophy. There also appears to be some confusion concerning the lipoid content of the cortical cells during this compensatory atrophy. Flexner and Grollman¹⁸ stated that the functional inactivation of the cortex is accompanied by a decrease in its lipoid content, while Dalton, Dosne and I¹⁹ came to exactly the opposite conclusion, stating that the cortical cells of rats treated with desoxycorticosterone are especially rich in lipoid granules. Furthermore there is some contradiction regarding the sex specificity of the adrenal response. Ingle²⁰ stated that in the rat cortical extracts cause more pronounced involution of the adrenal cortex in males than in females. On the other hand, I,⁸ who used desoxycorticosterone acetate, found the female adrenal to be more responsive, a fact

adrenals. In this respect her conclusions are in contradiction to those of Gersh and Grollman,²³ who stated that cortex extracts and desoxycorticosterone acetate inhibit development of the X zone in immature animals. In view of these contradictory results, I decided to

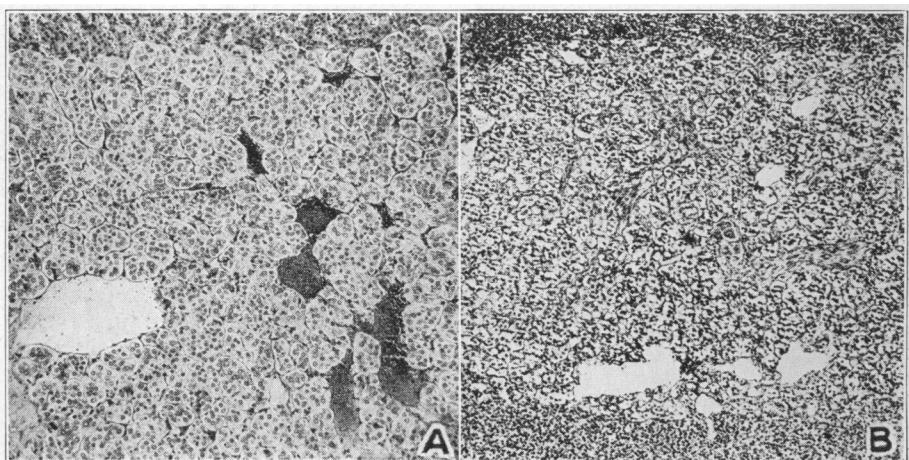


Fig. 3.—A, adrenal medulla of normal control female rat. B, adrenal medulla of female rat treated with desoxycorticosterone at same magnification as in A. Note shrinkage and vacuolization of medullary cells and scattered strands of dense connective tissue.

15. Ingle, D. J.: Am. J. Physiol. **124**: 369 (Nov.) 1938; footnotes 20 and 24. Ingle and Kendall: Ingle, Higgins and Kendall: *ibid.*

16. Kendall, E. C.: Read before the meeting of the American Society of Biological Chemists, New Orleans, March 13-16, 1940.

17. Selye, Hans, and Dosne, Christiane: Proc. Soc. Exper. Biol. & Med. **44**: 165 (May) 1940. Selye,⁸

18. Flexner, L. B., and Grollman, Arthur: Anat. Rec. **75**: 207 (Oct. 25) 1939.

19. Dalton, A. J.; Dosne, Christiane, and Selye, Hans: Read before the meeting of the American Association of Anatomists, Louisville, Ky., March 20-22, 1940.

20. Ingle, D. J.: Endocrinology **20**: 194 (Feb.) 1939.

reinvestigate this problem in both the rat and the mouse. My first series consisted of a number of experiments performed on 2 to 3 month old albino rats. In every case desoxycorticosterone acetate and all other steroids were administered in daily doses of 10 mg. subcutaneously, this amount being dissolved in 0.4 cc.

21. Robson, J. M., and Taylor, H.: Proc. Roy. Soc., London, s. B **113**: 251, 1933.

22. Howard, Evelyn: Read before the meeting of American Physiological Society, New Orleans, March 13-16, 1940.

23. Gersh, I., and Grollman, Arthur: Anat. Rec. **75**: 131 (Oct. 25) 1939. Hinteregger, F.: Beitr. z. path. Anat. u. z. allg. Path. **87**: 555, 1931.

of pure peanut oil. In all instances the melting points of the steroids were determined in order to ascertain that the samples were sufficiently purified. With the exception of the pregnenolone, a technical preparation having a melting point of 183 C. instead of from 189 to 190 C., all melting points were correct.

It appears from the results summarized in this table that desoxycorticosterone acetate has a very pronounced effect on the adrenals, whose total weight it decreases significantly in both sexes. The atrophy reaches its maximum after ten days and does not become more severe if treatment is continued for another ten days. It is also evident from table 1 that, although the females are somewhat smaller than the males in a series such as this in which all animals were of approximately the same age, the adrenals are heavier in the former. Microscopic examination shows that this difference is due almost entirely to the larger size of the cortex in the female. This explains why desoxycorticosterone causes a more pronounced loss in the weight of the female adrenal, since it decreases the amount of cortical tissue to a minimum, and in the case of the female there is more cortical tissue in which the atrophy can show itself. Thus in table 1 it will be seen that the weight of the adrenals decreased to the average of from 19 to 22 mg. in all groups treated with desoxycorticosterone acetate, irrespective of sex or length of treatment. In order to establish whether this action of desoxycorticosterone acetate is specific, a number of other sterols were tested for their adrenal activity and the table indicates that neither cholesterol nor pregnandiol or pregnenolone has any such effect, so that it seems justified to assume that this action is not merely due to the introduction of a certain amount of any steroid substance. On the other hand, Δ^5 -dehydro-*iso*-androsterone caused a significant decrease in adrenal weights in the females. As this compound is an active androgen, I shall discuss this finding later, with the action of other androgens.

Microscopic examination of this material revealed that all three zones of the adrenal cortex participate approximately equally in the atrophy of the organ. In this respect the histologic structure of the cortex is very different indeed from that of a hypophysectomized animal. After ablation of the pituitary the zona reticularis is the first to undergo atrophy; in fact its degeneration is usually so rapid in the rat that numerous hemorrhages appear in this region. No such change is visible in the animals treated with desoxycorticosterone (figs. 1, 2 and 4). It is not easy to understand this difference in appearance because the most logical explanation of the mechanism responsible for this compensatory atrophy is to assume, as Ingle²⁴ suggests, that it is due to a decrease in the production of adrenotropic hormone. Yet if this were correct the appearance

of the cortex should be the same whether the atrophy is caused by surgical removal of the anterior lobe or by hormonal inhibition of its adrenotropic hormone production. It is noteworthy that the lipoid content of the atrophic cortical cells was always very high in the rats treated with desoxycorticosterone as long as degeneration did not proceed too far.

Although the medulla showed no conspicuous decrease in size, microscopic examination indicates that it also is affected. Its cells are vacuolated and show signs of degeneration. In many instances the connective tissue stroma undergoes marked proliferation between the endocrine cell cords (figs. 3 and 5). It is conceivable that the medullary changes are merely the consequence of the decreased blood supply which reaches the adrenals as a sequel to the cortical atrophy, since most of the arterial vessels which supply the gland break up into a capillary network in the cortex before reaching the medulla. Yet in hypophysectomized animals whose cortex is likewise atrophic such medullary changes are

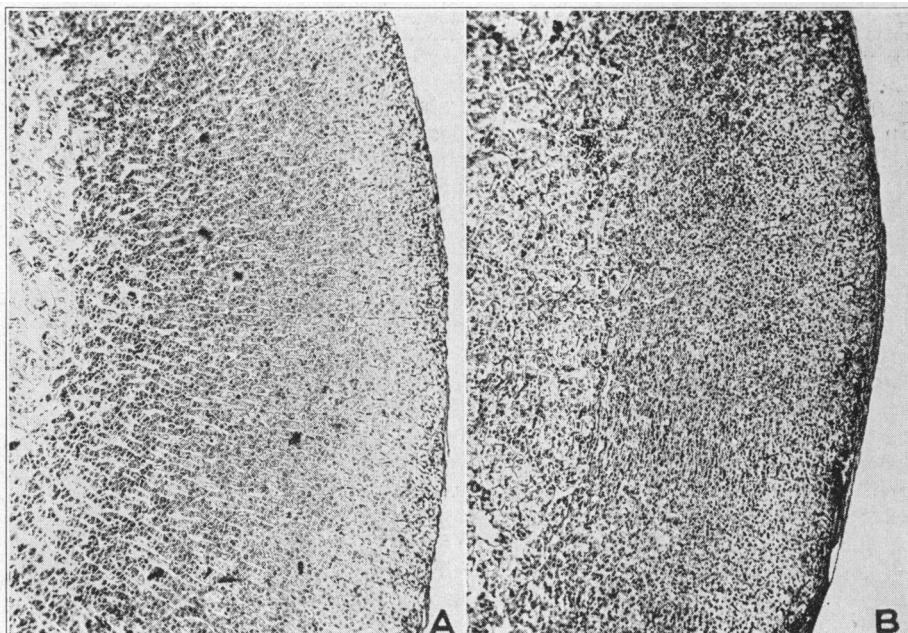


Fig. 4.—A, high magnification of adrenal cortex in normal control male rat. B, adrenal cortex of desoxycorticosterone acetate treated male rat at same magnification as in A. Note marked atrophy of all cortical layers.

not commonly observed. Whatever the mechanism of these medullary changes may be, they seem to represent a typical example of "transferred compensatory atrophy."

The action of desoxycorticosterone acetate on the X zone of the mouse adrenal was studied in a group of 1 month old albino mice. In this strain the X zone is always well developed in normal females and castrates of both sexes but is absent in normal males, presumably because the presence of an active testis makes the function of this androgenic tissue unnecessary. Both desoxycorticosterone and cholesterol which was used for control purposes were administered during twenty days in daily doses of 3 mg. subcutaneously in peanut oil. The results are summarized in table 2. From this table it appears that in the mouse as in the rat the adrenals are larger in the female than in the male, and this sex difference is not completely eliminated by gonadectomy. Desoxycorticosterone acetate causes a marked reduction in the total weight of the gland in gonadectomized animals of both sexes, and microscopic examination shows that this is accompanied by com-

24. Ingle, D. J.: Am. J. Physiol. 124: 627 (Dec.) 1938.

plete disappearance of the X zone (figs. 6 and 7A). It appears therefore that this compound, which is not a testis hormone, is capable of causing involution of the presumably androgenic zone. If it should prove correct that the X zone is functionally different from the remaining cortex and is the source of adrenal androgens, one would have to consider this change to be

TABLE 2.—*The Action of Desoxycorticosterone Acetate on Adrenal Weights in Mice*

Material Injected	Number of Mice	Sex	Body Weight, Gm.	Adrenal Weight, Mg.	Significance Change *
Not injected.....	6	♂	24	3.5	—
Not injected.....	6	Castrate ♂	20	3.7	P = 0.6
Cholesterol.....	6	Castrate ♂	21	3.2	P = 0.5
Desoxycorticosterone acetate	6	Castrate ♂	21	2.7	P = 0.04
Not injected.....	6	♀	22	4.8	—
Not injected.....	6	Spayed ♀	21	4.7	P = 0.7
Cholesterol.....	6	Spayed ♀	23	4.4	P = 0.3
Desoxycorticosterone acetate	6	Spayed ♀	21	2.6	P = 0.03

* The significance of the apparent differences has been calculated, the noninjected castrates being used as controls for the treated castrates and the noninjected intact animals as controls for the noninjected castrates.

another example of "transferred compensatory atrophy." In any case the microscopic appearance of the cortical cells was such in all zones of the organ that it seems very probable that their ability to produce hormones other than desoxycorticosterone was likewise impaired, the atrophy appearing to be "transferred" even in this respect.

THE ACTION OF PROGESTERONE

Using relatively small doses (2 mg. a day) of progesterone, I⁸ obtained only slight adrenal atrophy in female rats and none in males. Clausen²⁵ was unable to produce a statistically significant decrease in the adrenal weights in this species, but this might have been due to the fact that he used relatively small doses. In the mouse, Starkey²⁶ asserted, without having experimental evidence to support his assertion, that progesterone might cause involution of the X zone. This has been contradicted by Martin,²⁷ Tolenaar²⁸ and Howard,²² who stated that progesterone in daily doses up to 5 mg. causes no change in the X zone of the adrenal in immature mice. Hence it was concluded that this hormone cannot be made responsible for the physiologic involution of this zone during gestation.

In view of the fact that the experiments mentioned in the previous section showed definitely that desoxycorticosterone causes marked adrenal atrophy, it appeared of special interest to establish whether progesterone, which differs from the latter only in the absence of one -OH group on C atom 21, would have the same effect. For this purpose 12 female albino rats weighing on the average 107 Gm. were divided into two groups of 6. The first group received only 0.4 cc. of peanut oil subcutaneously daily; the second group was injected with 10 mg. of progesterone in the same amount of oil. After twenty days of treatment, all animals were killed. The average adrenal weight in the control group was 40 mg. at this time, while in the progesterone-treated group it was only 29 mg. This decrease is obviously statistically significant since P < 0.01. Another experiment of this type was performed on 12 castrate male albino rats weighing 175 Gm. on the

average. Here again 10 mg. of progesterone was administered daily in 0.4 cc. of peanut oil to one group while the other group was treated merely with peanut oil. The average adrenal weight was 40 mg. in the controls and 36 mg. in the progesterone-treated group. However, this decrease was not statistically significant since P = 0.3. The reason progesterone failed to cause more significant atrophy in this group is probably that these animals were much heavier than those of the previous group and yet received the same dose of the substance. Several other experiments in which we studied the action of progesterone confirmed these observations, as they showed that this compound causes some decrease in adrenal weight but is much less potent in this respect than desoxycorticosterone.

In 6 gonadectomized female albino mice having an average body weight of 21 Gm., daily administration of 3 mg. of progesterone caused a decrease in the average adrenal weight from 4.7 to 3.8 mg. (P = 0.05), while in 6 males of the same size the average adrenal weight of the noninjected castrates (3.7 mg.) was approximately the same as that of the progesterone-treated animals (3.9 mg.). These results confirm the view expressed in our previously quoted paper, namely that the female organism is more sensitive to this action of progesterone than the male. At the same time a comparison of the atrophy produced in these groups with the decrease in adrenal weight caused by treatment with desoxycorticosterone acetate under exactly identical conditions (see the previous section of this communication) shows beyond doubt that the slight change in the molecular structure of desoxycorticosterone which results in its transformation into progesterone greatly reduces its ability to cause adrenal atrophy.

Microscopic studies of the adrenals of progesterone-treated rats showed lesions which were essentially similar to those elicited by desoxycorticosterone but were much less pronounced. In the gonadectomized

TABLE 3.—*Inhibition by Various Steroid Compounds of the Adrenal Hypertrophy Caused by Estradiol*

Material Injected	Number of Rats	Sex	Adrenal Weight, Mg.	Significance of Adrenal Weight Change *
Not injected.....	6	♂	35	Control
Estradiol.....	6	♂	48	P < 0.01
Estradiol and progesterone.....	6	♂	39	P = 0.03
Estradiol and testosterone.....	6	♂	41	P < 0.01
Estradiol and desoxycorticosterone acetate.....	6	♂	39	P = 0.02
Not injected.....	6	♀	42	Control
Estradiol.....	6	♀	48	P = 0.1
Estradiol and progesterone.....	6	♀	47	P = 0.1
Estradiol and testosterone.....	6	♀	43	P = 0.5
Estradiol and desoxycorticosterone acetate.....	6	♀	46	P = 0.7

* The statistical significance of the apparent change in adrenal weight is expressed in comparison with the noninjected normals in the case of the animals treated with estradiol alone. In all other cases the result of combined treatment with two compounds is compared with that of mere estradiol administration.

mouse, the most conspicuous result of progesterone therapy was the disappearance of the X zone in both sexes (fig. 7B).

THE ACTION OF ANDROGENS

While most investigators agree that the X zone of the mouse adrenal disappears under the influence of androgens,²⁹ no significant change in the weight or histologic structure of the adrenal has been observed

25. Clausen, H. J.: Read before the meeting of the American Association of Anatomists, Louisville, Ky., March 20-22, 1940.
 26. Starkey, W.: Univ. Pittsburgh Bull., October 1937, vol. 34.
 27. Martin, S. J.: Proc. Soc. Exper. Biol. & Med. 28: 41, 1930.
 28. Tolenaar, J.: Acta brev. neerl. 9: 54, 1939.

29. Poll, Heinrich: Deutsche med. Wochenschr. 59: 567 (April 14) 1933; Anat. Anz. 77: 113, 1933. Martin,²⁷ Howard,²²

in lizards,³⁰ guinea pigs³¹ and dogs.³² Vidgoff and Vehrs³³ stated that in the rat the so-called inhibitory hormone of the testis, which causes involution of the male sex organs, leads to hypertrophy of the adrenal cortex. However, I³⁴ demonstrated that all nonspecific agents which cause gonadal atrophy also produce enlargement of the adrenal cortex, and therefore it appears very probable that the relatively crude testis extracts employed by Vidgoff and Vehrs owe both their adrenal enlarging and sex organ inhibiting actions to their toxicity. Crystalline testosterone causes definite adrenal atrophy in immature females³⁵ and a less pronounced decrease in adrenal weight in adult females,³⁶ but no such decrease could be obtained in adult males.⁸ It is of interest that in the case of early postnatal treatment with testosterone propionate the cortical atrophy is particularly marked in the rat but is due mainly to involution of the glomerulosa.³⁷ In this respect the atrophy differs qualitatively from that produced by hypophysectomy, which, as I mentioned before, is characterized by a predominant reticularis atrophy.

Since the adrenals are smaller in males than in females, the fact that a definite decrease in adrenal weight was obtained only by androgens in female rats might be regarded as an indication that this change is due merely to a "masculinization" of the female. In order to test this possibility my associates and I performed an experiment in a group of 12 newborn albino male rats, 6 of which received 1 mg. of testosterone daily during twenty-four days, beginning on the day of birth. The dose was then raised to 3 mg. daily, the animals being killed on the thirtieth day of treatment. The remaining 6 rats received the same dose of cholesterol during this period and served as controls. The experiment was performed on such immature animals because previous observations taught us that it is easier to inhibit the development of the adrenal than to cause atrophy of a fully developed gland. The average adrenal weight in the controls was 24 mg. as compared with 12 mg. in the testosterone-treated group. The decrease was obviously statistically significant, since even the largest adrenal in the testosterone group was considerably smaller than the smallest of the control glands ($P = <0.01$). This experiment indicates perhaps that one is dealing not merely with a "masculinization" but with true compensatory atrophy, although it is not impossible that the gonads of such

immature males produce so little—if any—androgen that the treatment may be regarded as "masculinization" of a neutral type.

Experiments on 6 castrate male and 6 spayed female 1 month old albino mice with an average body weight of 22 Gm. showed that daily administration of 3 mg. of testosterone during a period of twenty days caused no change in the average adrenal weight of the males (3.7 mg.), but in the females the average weight of the organ decreased from 4.7 to 3.8 mg. ($P = 0.06$). Microscopic examination showed that irrespective of the adrenal weight the X zone disappeared under the influence of the androgen in both sexes (fig. 8).

These results indicate that androgens have a definite effect on the adrenal cortex, a conclusion which receives further support through the observations recorded in table 1, that dehydro-iso-androsterone is also active in decreasing the adrenal weight of the female rat.

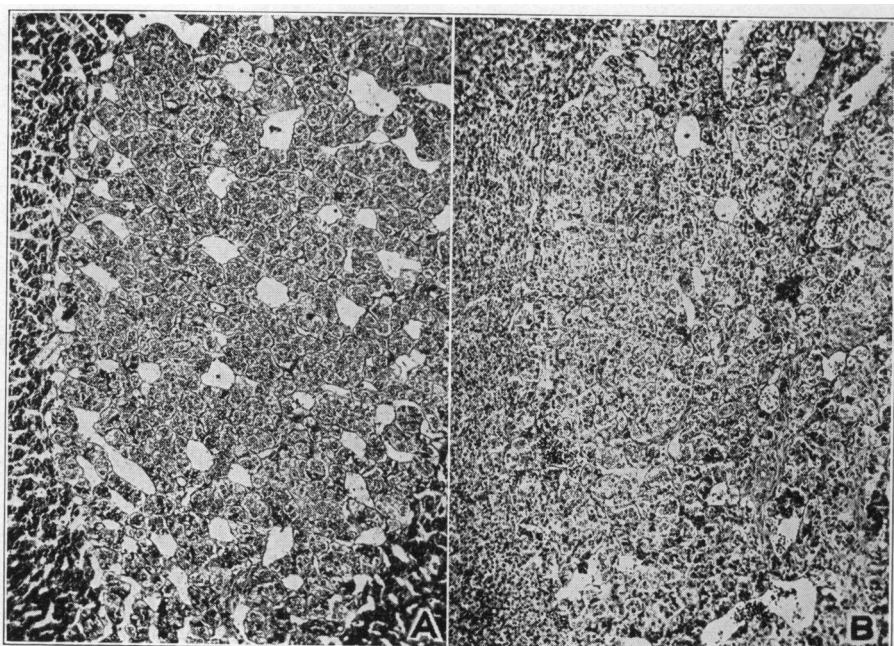


Fig. 5.—A, high magnification of medulla of normal control male rat. B, adrenal medulla of male rat treated with desoxycorticosterone acetate at same magnification as in A. Note marked vacuolization and involution of medullary cells.

PREVENTION OF VARIOUS TYPES OF HYPERPLASIA OF ADRENAL CORTEX BY MEANS OF STEROID HORMONES

Although early investigators who used impure preparations of estrogens obtained contradictory results,³⁸ Selye, Collip and Thomson³⁹ showed that crystalline estrone causes marked hypertrophy of the adrenal cortex in the rat, a fact which has since been confirmed for numerous other estrogens. It appeared of interest to establish whether this hypertrophy may be prevented by other steroid hormones. For this purpose a series of experiments was performed on albino rats. The average weight of the males was 154 Gm. and that of the females 109 Gm. All experimental animals were treated with daily doses of 300 micrograms of alpha-estradiol while the other steroid hormones were administered in daily doses of 2 mg. The daily dose of each of these com-

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39. Selye, Hans; Collip, J. B., and Thomson, D. L.: *Proc. Soc. Exper. Biol. & Med.* **32**: 1377 (May) 1935.

pounds was injected subcutaneously in 0.1 cc. of peanut oil during a period of twenty days. The results of the experiments are summarized in table 3. The table indicates clearly that progesterone, testosterone and desoxycorticosterone are all capable of inhibiting the estradiol hypertrophy of the adrenal in males in which estradiol induced a significant cortical enlargement. In the females, the adrenals of which are larger than those of the males under normal conditions, the 300 microgram dose of estradiol used in these experiments led to no statistically significant adrenal weight increase and consequently the other steroids could not show a significant inhibition.

The fact that the adrenal enlargement normally produced by muscular exercise may be prevented by cortex extracts has been demonstrated by Ingle.²⁴ My associates and I¹⁰ found that desoxycorticosterone, testosterone and progesterone may also prevent the adrenal enlargement caused by various other damaging agents such as injections of formaldehyde and surgical shock. Since during the alarm reaction elicited by such stimuli as muscular exercise, trauma or toxic doses of drugs the pituitary responds with an increase in adrenotropic hormone production¹⁰ and the aforementioned steroids inhibit the elaboration of the adrenotropic principle by the pituitary, it is concluded that the inhibition of adrenal enlargement under these conditions is probably mediated by the hypophysis.

SUMMARY AND CONCLUSIONS

Experimental evidence indicates that both in the mouse and in the rat desoxycorticosterone acetate causes marked involution of the adrenal cortex. Histologically the atrophy of the cortical cells is very pronounced in all three zones, yet unlike the atrophy caused by hypophysectomy it is not particularly severe in the zona reticularis. Although it appears quite probable that the action of this cortical steroid is due to its ability to inhibit production of adrenotropic hormone, this observation is not easily reconcilable with such an interpretation. The cells of the adrenal medulla become vacuolated and show signs of degeneration in rats treated with desoxycorticosterone acetate.

In the gonadectomized male or female mouse the characteristic X zone of the cortex disappears under the influence of desoxycorticosterone acetate. Changes in the medulla are not readily detectable in this species.

Progesterone given in large doses also causes involution of the adrenal cortex in the rat and to a lesser degree in the mouse. This effect is evident only in females, and even in these much higher doses have to be administered to obtain an atrophy comparable to that caused by desoxycorticosterone acetate. The X zone of the mouse adrenal disappears in gonadectomized males or females treated with progesterone.

Androgens such as testosterone or Δ^5 -dehydro-*iso*-androsterone are also capable of causing involution of the adrenal cortex, again much more readily in females than in males. The disappearance of the X zone, which is obtained by androgens in gonadectomized mice, is not always accompanied by a measurable decrease in adrenal weight.

Estradiol causes much more pronounced hypertrophy of the adrenal cortex in male than in female rats. This effect is inhibited by the simultaneous administration of desoxycorticosterone acetate, progesterone or testosterone.

The atrophy of an endocrine gland caused by the administration of an excess of the hormone or hormones which it produces is regarded as the exact antithesis of the compensatory hypertrophy elicited by the hormone deficiency occasioned by partial extirpation of such a gland. For this mechanism of readjustment the term "compensatory atrophy" is suggested. It is essentially the same mechanism which in human pathology is responsible for instance for atrophy of the adrenal cortex if a tumor develops in the cortex of the contralateral adrenal gland. Experimental work shows that such compensatory hypertrophy may in some instances be produced by substances other than the main product of secretion of a certain endocrine gland. Thus atrophy of the testis has been elicited with estrogens or progesterone, atrophy of the adrenal cortex with androgens or progesterone, involution of the adrenal medulla with desoxycorticosterone acetate and the like. In these cases, one is dealing with a "transferred" compensatory atrophy. This phenomenon promises to be of clinical importance, since it may afford a means by which to decrease the activity of overfunctioning endocrine glands without having to administer additional amounts of a substance which is already produced in excess. Thus, for instance, the use of desoxycorticosterone acetate (a substance which is practically devoid of androgenic activity) in cases of adrenogenital syndrome in which there is an excess production of androgen in the adrenal may prove useful in inhibiting the faulty endocrine secretion of the cortex.

ABSTRACT OF DISCUSSION

DR. J. P. SIMONDS, Chicago: Some years ago Dr. O. E. Hepler, working in our department on fat tolerance in experimental hyperthyroidism, demonstrated both anatomic and physiologic evidence of compensatory atrophy. After dogs had been fed large doses of desiccated thyroid for several weeks the thyroid gland became so small that it was often difficult to find it. When such feeding was stopped, the cholesterol of the blood rose within two weeks to the high levels characteristic of myxedema and other forms of hypothyroidism. I should like to ask Dr. Selye if he has made any observations on the permanence of this compensatory atrophy.

DR. MILTON STEINBERG, Chicago: I would mention in connection with this paper that in all probability the results were mediated through the anterior pituitary; that the results were not directly through flooding the system with the hormone but through suppressing the pituitary. I think that this work should be checked by examining the anterior pituitary microscopically and should also be checked in animals with the anterior pituitary removed; I doubt whether the effect would be present in that case.

DR. HANS SELYE, Montreal, Canada: With regard to the permanence of the lesions, I experimented only with testosterone and found that its actions are still detectable months after injections were discontinued. However, I don't believe the change would be permanent in the true sense of the word and I suppose that after a still longer period recovery would ensue. With regard to the statement that the adrenal atrophy induced by steroid hormones is indirect and mediated by the pituitary, I should like to state that this is quite in accordance with my own opinion; in fact, I have experimental evidence to prove this point. It was shown that if a hypophysectomized rat receives sufficiently large doses of adrenotropic hormone to maintain the adrenal in a normal condition, none of the steroids mentioned are able to cause cortical atrophy. This, I feel, shows distinctly that the steroids act mainly, if not entirely, by depressing the adrenotropic hormone secretion of the hypophysis. The only observation which would seem to plead against this interpretation is that the microscopic appearance of the cortex following atrophy induced by testosterone or desoxycorticosterone differs from that seen in hypophysectomized rats, a fact illustrated by the lantern slides.

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