

## ORIGINAL COMMUNICATIONS

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### RECENT VIEWS AS TO THE FUNCTION OF THE ADRENAL BODIES

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**I**F we hope to gain any exact information as to the diseased conditions of the adrenal bodies, the clinical disturbances which arise from such conditions, and the rational treatment of them, it is essential that we keep in mind the most recent and the most matured observations relating to the physiology of these bodies.

No attempt will be made in this place to deal with the whole subject of the functions of the adrenal bodies. The object of the present communication is to emphasize certain broad conceptions and to discuss certain fundamental topics in accordance with the results of the most recent investigations.

It is certain that in lower vertebrates the cortex and the medulla constitute representatives of two separate and independent series of organs, and there is no reason to suspect any physiological relationship between the two. In mammals a mass of chromaphil cells has become enclosed in the adrenal (or "cortex") and we have thus formed what we know as the adrenal body.\*

Whether this partial coming together of the two systems in higher animals has any physiological importance we do not know. On the whole the safest

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\*It must be remembered, however, that even in mammals, there are outstanding portions of the original chromaphil bodies and of the original cortical bodies.

attitude is one in which the assumption is made provisionally that the two portions, cortex and medulla, have separate and independent functions. At any rate there is no good evidence of an experimental or clinical nature which warrants us in believing that the adrenal body as a whole has any definite functions. We know nothing of the functions of the adrenal body regarded as an organ on its own account.

Modern works for the guidance of practising physicians are often very confused on this point. Thus Falta (6) says: "Already at an early period some of the chromaffin cells have broken through the complex of cortical cells to form the medulla. Through the descent of the genital organs small parts of both systems are displaced. This shows that the former complete physiological independence of both systems later gives place to a common function, at least in part (Biedl), which fact is also indicated by the previously mentioned relations of the blood-vessels. It is indispensable for the comprehension of diseases of the adrenals to consider that the two systems for a great part are functionally independent. The higher we go in the classes of animals, the greater become the complexes of the two systems that finally unite to form a single organ, the adrenal."

Now the present writer begs to submit that the fact that certain masses of chromaphil cells break into the interior of the cortex does not prove that any functional relation between the two becomes established, nor does the fact that through the descent of the genital organs small parts of both systems are displaced, bear upon the point. The same may be said of the relations of the blood-vessels. But in the next sentence it is urged that "the two systems for

a great part are functionally independent." Finally the writer returns to the idea of a single organ. Surely the matter would have been clearer if the writer had merely expressed a doubt as to any possible physiological connection between the two systems.

It seems to be well established that total extirpation of both adrenal glands will invariably cause death of the animal.\* The question naturally arises whether death is to be attributed to loss of the cortex, or of the medulla, or of both of these. In the work of Falta above referred to we do not find any adequate statement of our present knowledge of this subject. The author says: "The sure knowledge that the cortical system and chromaffin system are in like manner important for life was first mentioned by later investigators (I mention only Biedl and Hultgren and Andersson)† who took into consideration the presence of accessory adrenals."

Now, in the first place, there is no "sure knowledge" that the cortical system and the chromaphil tissue are in like manner essential for life. There is, in fact, every reason to believe that such is not the case. Biedl, whom Falta quotes, has urged very strongly that it is the cortex and not the medulla (or the chromaphil tissue) which is essential to life. This investigator found that rabbits and dogs would survive removal of all but one-eighth part of both adrenal bodies, provided that the portion remaining consists of cortex. (4) He found also that removal of the interrenal body of elasmobranch fishes is uniformly fatal. Many years ago the present writer (18,

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\*A few exceptions to this rule have been recorded, but they scarcely affect the essential validity of the thesis.

†I have made minor but essential corrections in quoting.

19) attempted to solve the problem by extirpation of the corpuscles of Stannius from the eel. But the negative results which were obtained were later fully explained by the discovery of a second cortical representative. This discovery was made by Giacomini (7) who described a mass of cortical adrenal cells in the "head kidney" of teleostean fishes.

The results obtained by Biedl were recently confirmed by Wheeler,\* who carried out a series of experiments in my laboratory. An attempt was made to remove the medulla of both adrenal bodies from a number of dogs, leaving the cortex undamaged. This was not precisely achieved, but it was found that the only fatal cases† were those in which very considerable damage had been done to the cortex as well as to the medulla. In some cases the abdominal chromophil body (Vincent, 20) was removed as well as the adrenal medulla. Of course in such experiments groups of sympathetic chromophil cells, as well as scattered cortical "accessory" bodies must be left behind. But this fact does not seriously affect the logic of the argument that it is the cortex which is essential to life. For, since removal of both adrenals is fatal, and removal of the medulla alone is not, it follows that the cortex is the essential part of the gland so far as the maintenance of life is concerned.

After the epoch-making discovery of Schafer (15, 16) that adrenal extracts raise the blood-pressure, there was a growing tendency to assume that the function of the adrenal (or, at least, of its medullary portion) is to help to maintain the normal blood-

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\*Results not yet published.

†At any rate among the animals which died of adrenal insufficiency.

pressure and to keep up the tone of sympathetically innervated structures in general. The present writer was one of the first to grow suspicious on this point. If the constant secretion of adrenin into the bloodstream and its action upon the sympathetically innervated vascular muscle is an important factor in the maintenance of the normal blood-pressure, then it ought to be possible by tying or clamping the veins issuing from the glands, to keep down the blood-pressure at a low level during the period of clamping or tying, and to allow it to reach its normal level on releasing the clamp or the ligature. Some writers have claimed that they have obtained this result. But Young and Lehmann (22), working in my laboratory, made an attempt in dogs to dam back any secretion which the glands may pour into the bloodstream, and, after an interval, to remove the obstruction, and allow the accumulated adrenin to flow into the general circulation. A cannula was inserted into the carotid artery, the adrenal glands were exposed through an abdominal incision, and a double ligature passed beneath the organ on each side; the ligatures were tied on each side of the gland above the vein, so as to form two pedicles. The ligatures were left in place for from ten to thirty minutes, and then released, and the blood-pressure tracing continued.

Out of eight experiments, there was no effect on the blood-pressure in three; in two there was a slight rise after releasing the ligatures; in the remaining three there was a decided rise of pressure (comparable with that which follows injection of adrenin into the circulation) lasting about three minutes. In one case the effect was repeated by tightening the ligatures a second time, and then releasing them.

It is important to note that in these experiments after tightening the ligature there was very little, if any, fall of blood-pressure. In fact the experiments merely show that adrenin is poured out into the adrenal veins.

Dr. Young (23) repeated these experiments and found that even after the lapse of several hours with the blood from the adrenal bodies absolutely excluded from the circulation, there was no appreciable fall of blood-pressure. During last winter Austmann and Halliday\* at my suggestion performed a series of experiments in which the adrenals were removed or whose vessels were tied off while the blood-pressure was continuously recorded for many hours. It was found that when the experiment was continued until the animal died the blood-pressure curve was not appreciably different from that obtained from an animal simply kept under ether as long as possible. These experiments appear to show conclusively that the secretion of adrenin into the circulation is not to be regarded as a factor in the maintenance of the normal blood-pressure.

But there is another argument which militates powerfully against the theory just mentioned. It was shown by Moore and Purinton (13) that very small doses of adrenin will lower the blood-pressure, not raise it, so that the amount of adrenin which is normally poured out by the adrenal veins would tend to keep the blood-pressure down rather than up.

It is difficult, indeed, in face of the foregoing consideration, to adduce any satisfactory evidence that the secretion of the chromophil tissue is of any use

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\*Results not yet published.

whatever in the normal state of the animal. (Hoskins, 11.)

But the suggestion has been made that the secretion is of great service in certain emergencies. Certain experiments of Cannon and de la Paz (5) seem to show that during times of emotional stress the adrenal bodies pour into the blood sufficient adrenin to be of some service, possibly in increasing the power of sustained muscular activity. This view has received very general approval, but it would be rash to affirm that it has been firmly established. Stewart and Rogoff (17) conclude that fright has nothing to do with the results.

The experiments of Hoskins and McClure (12) taken in conjunction with others above referred to, furnish sufficient evidence to warrant us abandoning the tonus theory of adrenal secretion. But the theory is still put forward by Falta (p. 345) and is made to account for the low blood-pressure in Addison's disease.\* The fact is that we have not a single physiological observation (except perhaps the effect of adrenin on the contraction of skeletal muscles†) which throws any light on the pathology of Addison's disease.

The question naturally arises, "Why is extirpation of the adrenal cortex fatal?" The answer is simply that we do not know. It is suggested by Hoskins (11) that muscular metabolism may be at fault.

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\*Falta's book is so extensively used by physicians and students that it is necessary to refer to its extraordinary deficiencies in the sections that bear upon physiological questions. Thus it is pointed out (p. 273) as something significant, not to say extraordinary, that extracts of the glandular portion of the pituitary body lower the blood-pressure. The Author and the Translator seem to be unaware that extracts of all organs and tissues have a similar action. (See Vincent 21, p. 24.)

†First observed by Oliver and Schafer. (15)

Some interesting experiments were carried out many years ago by Abelous and Langlois (1, 2, 3). This was in 1892, some few years before the discovery by Oliver and Schafer that adrenal extracts raise the blood-pressure. The French authors found that intravenous or subcutaneous injection of the blood of a frog dying after adrenal extirpation into a frog recently deprived of the glands, induced rapidly developing paralysis and death. The same injection into a normal frog only gives rise to slight temporary symptoms. Their theory was that death after extirpation results from the accumulation in the blood of one or several toxic substances, and that the adrenal bodies are capable of elaborating a substance which neutralizes the toxic effects of such substances. These observations were in the main confirmed by Gourfein (8, 9, 10), but have not received much attention by recent writers. The matter has recently been investigated by Hoskins (11), who finds that the blood of dogs that have just died of adrenal deficiency is in no degree toxic when administered to frogs.

That the cortex may exert antidotal properties was suggested by Myers' (14) observation that cobra poison, after being mixed with an emulsion of the adrenal cortex, was no longer toxic. There are a few other isolated records which seem to point in the same direction, but it must be confessed that the anti-toxic theory has not been substantiated.

The following is a brief summary of what, in the opinion of the present writer, represents the state of our knowledge concerning the adrenal bodies:

1. What we call the adrenal body represents the anatomical association of two elements, each one of which is derived from a separate and independent

system. The adrenal body proper or cortex is part of the "cortical" or "interrenal" system. The medulla is simply an accumulation of chromaphil cells of the same nature, histologically, chemically, and pharmacodynamically, as similar but smaller masses along the sympathetic at other levels.

2. There is no clear evidence that these two systems are functionally related to one another.

3. The adrenal medulla (as well as the "chromaphil tissue" generally) is derived from the sympathetic nervous system, and is alleged to facilitate this system's functions in certain physiological emergencies.

4. The cortex is derived from the germ epithelium and there is considerable evidence that it has important functions in connection with the development of the reproductive organs.

5. There is a considerable mass of clinical evidence that tumors of the adrenal cortex are frequently associated with sex abnormalities.\*

6. Additional evidence in the same direction is furnished by the enlargement of the cortex during breeding and pregnancy.

7. It is possible that a final solution of the problem as to the relation between the adrenal gland and sex will only be arrived at when the wider problem of the relationships between the various ductless glands shall have been solved.

8. Feeding young animals with adrenal gland substance seems to stimulate the growth of the testis.

9. The cortex is the part of the gland which is essential to life. We do not know why its removal causes death, but it is possible that this is due to some defect in muscular metabolism.

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\*The association is frequent, though not constant.

10. The symptoms of Addison's disease are in no way explained by the accumulated results of investigations in the comparative anatomy and the experimental physiology of the adrenal bodies.

11. It is too early to attempt to diagnose clinically any syndromata due to hyper- or hypo-function of the adrenal bodies.

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## COMMENT ON PROF. VINCENT'S ARTICLE

**Prof. G. N. Stewart, Western Reserve University, Cleveland:** I have no comment to make upon Prof. Vincent's excellent summary, except perhaps to add another proof, obtained by Dr. J. M. Rogoff and myself, that the discharge of adrenin from the adrenal is not indispensable for life or health.

When one adrenal is removed (in the cat) and the nerves which are concerned in the liberation of adrenin from the other divided by Elliott's operation (Jour. Physiol., 1912, xliv, 374) the animal recovers from the operation and lives in apparently normal health, for an indefinite period. Nevertheless, it can be shown that the rate at which adrenin is given off under experimental conditions is very greatly reduced—to one-fiftieth or even one-hundredth of the normal rate. There are differences in the amount of the residual liberation in different experiments, these differences in all probability depending upon whether the secretory nerves have been more or less completely severed.\*

But in all the animals the discharge is enormously reduced, and, in some, the test employed (denervated iris, and, on drawn blood, rabbit intestine and uterus segments) have yielded no evidence of any adrenin in the blood coming from the remaining adrenal. In one cat, for instance, it was found that there was no clearly detectable content of adrenin in the adrenal blood, although by the most delicate of the tests employed, a concentration of 1:400 millions could have been detected. This, it must be remembered, was under experimental conditions which have been supposed to increase the liberation through the nervous

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\*It must be remembered that Elliott's operation (section of all the fibres coming to the semilunar ganglion) has never been shown to be equivalent to section of all the fibres concerned in the liberation of adrenin. What he showed was that it protected the corresponding gland against reduction of the adrenin store under the influence of morphin, tetrahydronaphthylamine, etc. This, of course, would be quite compatible with the existence of some undivided secretory fibres, since the adrenin formed might balance the discharge.

mechanism. In the mixed blood of the right heart the concentration could have been at most one-hundredth of 1:400 millions, which the most enthusiastic upholder of the physiological importance of adrenin will probably consider below the threshold of any definite physiological reaction. Yet the animal was in good health.

**Prof. R. G. Hoskins, Northwestern University Medical School, Chicago:** Professor Vincent has expressed exactly my views as to the present status of the adrenal problem; but I would add that there is no reliable evidence that under normal conditions circulating blood contains any adrenin at all. It is probably significant that as the technique of investigating the problem has improved the reported dilution of the adrenin in arterial blood has constantly approached infinity. Trendelenberg, using the very delicate frog perfusion method, found that there was present in the carotid blood of normal rabbits at most no more than one part in one or two billions,—a quantity well below the threshold of vasomotor stimulation in mammals. And Trendelenberg did not wholly exclude the possibility that the infinitesimal trace of material supposed to be adrenin was actually a vasoconstrictor substance derived from traumatized blood platelets.

Much confusion has arisen from ignoring the fact that the thoracico-lumbar (sympathetic) system can itself do anything that can be accomplished by adrenin. The adrenals at most merely reinforce the effect of normal sympathetic impulses. Therefore, to ascribe promiscuously conditions of low blood pressure to adrenin deficiency as is done by various clinical writers is quite without justification. The fact that adrenin may improve such conditions no more demonstrates their adrenal etiology than does the "therapeutic test" prove that *pulsus irregularis* is due to a deficiency of circulating digitalis. When to this unsubstantiated conception of sympathetic control

by adrenin is confidently added a theory that the automatic system is similarly dependent upon the beneficent influence of a hypothetical "hormone x" actual absurdity has been reached.

It is even possible that the adrenin problem is commonly regarded from the wrong end. Perhaps it is not the discharge but the formation of adrenin that is the important thing! It may be formed merely by way of rendering harmless some precursor that otherwise would serve as a slow metabolic poison. The fact that adrenin is found in an external secretion from the skin of certain toads supports that idea. Possibly except in times of stress the adrenin of the chromaffin tissue is changed in situ to an inert form and then discharged. This hypothesis could be extended to fit the known facts better than does the theory that adrenin serves normally to maintain the tonus of the sympathetic nervous system.