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"ON THE EXTIRPATION OF THE ADRENAL BODIES"..

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A. THE COMPLETE EXTIRPATION OF BOTH GLANDS".

1. HISTORICAL.

Addison (2), when in 1855 he associated the disease which bears his name with lesion of the suprarenal capsules, gave an immense impetus to research upon these organs. All that had gone before served as the basis for the really profound yet fantastical doctrines concerning the functions of these glands.

Bartholmeus Estachius Santoseverinatus, the anatomist, first described them in 1563. The work of the next three centuries supplied all that was to be known microsopically of the anatomy, a certain small amount of the embryology, and the pathogical histology. The keen research of the first half of the eighteenth century gave important data to the comparative morphology.

But no effort had been made at physiological research; that is to say, by direct experiment upon the living animal. True, Addison's observations from a clinical picture supplied the first contribution to the

physiology of the adrenals; they show that these glands are necessary to the life of the animal, and that lesion of them gives very characteristic symptons, namely, an idiopathic anemia associated with extreme apathy and adynamia, disturbances of the digestive tract and the nervous system, and a bronze coloured pigmentation of the skin and of the mucous membranes; whose course was chronic; which presented all the features of a progressive cachexia, frequently accompanied by violent symptoms, such as uncontrollable diarrhea, coma and convulsions. Addison reports, in every case which he examined, a serious disease, generally tubercular in character, of the suprarenal capsules. His conclusion was that the pathological conditions and the fatal terminations were due to the suppression of the function of these glands.

It was an effort to establish this disease artifically the experiments were carried out; naturally, the method adopted would be to extirpate, or in some other way produce a lesion of these glands.

2. PREVIOUS EXPERIMENTS.

Brown-Sequard (9) in 1856 was the first to publish any results of experiments upon animals. "He employed for the extirpation of both glands forty-four rabbits, nine guinea pigs, two rats, and several dogs and cats. All of these animals died in 9-37 hours after the operation. For the unilateral operation this experimenter used sixteen rabbits, five guinea pigs, two cats and two dogs. All of these died in 23-34 hours. Later he repeated the removal of one gland from two dogs, which survived for eight days". Vincent, "Internal Secretion". p. 134.

The following are the conclusions of Brown-Sequard;-

"La destruction des capsules surrénàles entraîne toujours la mort à plus ou moins brève échéance.

La destruction d'une seule capsule, bien au'assez souvent mortelle, n'est pas toujours suivie d'une issue fatale. Les capsules surrénals sont des organes essentiels á la vie.

La mort à la suite de l'alteration de des organes est précédée d'un affaiblissement graduel allant jusqu'à la paralysie des membres postérieurs, puis antérieurs, enfine des muscles respiratoires. On note encore l' anorexie, l'arrêt de la digestion, des convulsions tétaniformes et epileptiformes, enfin un abaissement graduel de la température". Langlois (18).

These views of Brown-Sequard were disputed by many men, notably Philipeaux, Martin Magnon, Chatelian, Harley, Gratiolet, Beruti and Schiff. These men worked for the most part between the years 1856 and 1863, and reported survival after total extirpation.

Philipeaux (24) worked with rabbits and white mice, and reported the survival of a number of these animals after complete bilateral extirpation. He claims that when death follows it is due to the operative conditions and complications such as peritonitis, damage to the nerve plexuses, and haemorrhage.

Martin Magnon (20) reported the survival of a cat for two months after complete removal of both glands.

Chatelain (10) after performing a number of experiments attributed the death to the damage done to the adjacent nerve plexuses.

"Harley (14) employed, among other animals, the white rat and found that they may survive the extirpation indefinitely". Vincent, "Internal Secretions," p. 135. He inferred from this that the death of other animals is due to damage to the neighboring plexuses.

Gratiolet (13) reported survivals after unilateral extirpation, but thought the death after the second operation to be due to trauma.

Berruti's (3) results agree with those of Gratiolet.

Schiff (26) at first was of the opinion that the glands were not necessary to life, but later is quoted by Gourfein, his pupil, as having changed his opinion; he based his initial view on the fact that he obtained a survival of a dog for three days.

Among the more recent experimenters who have disputed the views of Brown-Sequard may be mentioned Burg in 1863, Nothnagel in 1879, Russe Giliberti et di Mattei, and Tizzoni in 1880. The work of these men is of special interest to this paper, as they were the first to use one of my methods of destruction, that is cauterisation.

"The work of Nothnagel (27) deserves special mention. This observer, from clinical data, thought that a chronic inflammation of the adrenals would be more likely to induce symptons resembling those of Addison's disease than would the removal of the glands. Accordingly he resorted to a method of crushing the bodies. He operated upon one hundred and fifty-three rabbits, and found that if the operations were performed upon the two sides, with an interval of three to four weeks, then the animals survived and showed no important symptons". Vincent, "Internal Secretion", p. 136.

"From the results of his experiments with dogs and rabbits, Tizzoni came to the conclusion that the destruction of one or both of the suprarenals is followed by death. He believed that death may occur soon after operation, or that it may be postponed for weeks and even months, and that it occurs as a result of serious changes of the central and peripheral nervous systems. He describes far-reaching disturbances of the nerve fibres and ganglion cells, accompanied by pronounced congestion, changes in the vessel walls, haemorrhages,

leucocytosis, infiltration into all parts of the nervous system. Tizzoni's experiments do not prove that the adrenals are essential to life, for his animals sometimes survived extirpation for months and even years. Moreover definite proof of relationship between the operative procedure and the post-mortem findings would have to be forthcoming. Such proof is lacking, and, in view of the method of operation employed, by which total extirpation of the suprarenals has rarely been accomplished, Tizzoni's experiments seem rather to show that animals with even serious lesion of the suprarenals may live for a long time without pathological signs, provided that these organs are not entirely destroyed.

Tizzoni's statements that, when one suprarenal or both were extirpated, and, in the latter case, whether they were removed together or singly, the results were in all cases the same, is a proof of the unreliability of his conclusions". Biedl, "Innere Secretion", p. 139.

An interesting piece of work was done by Boinet (8) upon the complete extirpation in white rats. He agreed with Harley, whom we have mentioned, that they will survive. This was explained by some authors as due to the large amount of accessory tissue that the rat possesses behind the renal veins. Boinet then extirpated the glands together with these accessory bodies, and reported fifty per cent survivals.

Wiesel (36), working a short time after with the same animals, found an accessory body between testis and the lower part of the epididymis; he states that, after complete extirpation, there can be demonstrated a compensatory hypertrophy of this body. It would seem according to these two writers, that the adrenals are not necessary to the life of the white rat.

The adrenals were stated by Krickpenko (16) to be unnecessary to life. He is of the opinion that other organs of the body may assume their function.

Moore and Puriton (21) have given the case of a goat which survived total extirpation for twenty-two days.

It is the opinion of the writer that these men are in a great measure justified for the ir views. If we consider the extreme difficulty of the operation, especially in regard to the right gland which lies very deep, directly behind the vena cava and completely overlapped by the posterior lobe of the liver, also the difficulty of keeping the ligatures on, the close relationship to the main nerve plexuses of the abdomen and the ease with which these are damaged, we can readily understand why they came to these conclusions.

On the other hand Brown-Sequard was supported by many careful experimenters.

Stilling (27) in 1890 was the first to do any important work. By his operations upon rabbits he was able to show that after the extirpation of one gland the other became much larger, that is, showed compensatory hypertrophy. According to him the average weight of the glands was 0.01g per 1Kg of body weight, but after the left had been

extirpated the right increased from the above to 0.17-0.43 g per Kg. This fact is a proof though rather an indirect one that the adrenals are necessary to life.

Stilling was the first to suggest the possibility of accessory adrenals in front of the vena cava, etc. In a measure he disagrees with Brown-Sequard, in that he suggests these to be sufficient for the life of the animal after the adrenals have been extirpated.

Abelous and Langlois (1) in 1891 did some very interesting work upon frogs. Their method was to destroy the gland which appears on the anterior surface of the kidney as a narrow, longitudinal red streak by cauterisation. They found that the total destruction of both glands was always fatal, but that the leaving of a quarter of each gland was sufficient to sustain the animal. When death occurred it was within twelve to thirteen days for winter frogs and within forty-eight hours for summer frogs.

I have repeated this work upon frogs. The animals employed were "intermediate" ones, i.e. neither winter nor summer. The glands were exposed from the front, and a heavy cautery used to destroy them. Out of fifteen animals, I report eight which were destroyed after a month, and a post-mortem examination of these showed four cases with absolutely no trace of the glands. Though it is to be regretted that I have not more clear cases to report, yet the results obtained are seen to be opposed to those of Abelous and Langlois.

From their work upon other animals, these men report death within forty-eight hours after complete extirpation; though if an interval of several days was allowed to elapse between the two operations necessary to remove the glands separately, then the survival time could be considerably lengthened.

Langlois (18), himself, in a brilliant series of experiments showed that animals will not survive for more than forty-eight hours after total extirpation. In this he is borne out by De Domincis (12) in 1893, Szymonowicz (31), Thiroloix (32),

Kudinzew (17) and Mariani (19). The results of these men all agree in time within a few hours as to the length of survival.

Hultgrun u. Andersson (15) in 1898, performed numerous reliable extirpation experiments. They report that cats die within one hundred and thirty-four hours after the operation removing both glands, while rabbits have been kept alive for as long as two weeks. They claim to have proven that the animals can be gradually educated to do without nearly all the glandular tissue; they give us as proofs that the animals live longer if the glands are taken out one at a time, still longer if they are taken out in three portions, and still longer if in four.

They also describe the symptons of removal as being very characteristic. "After the operation the animal recovers within a few hours, and in the first few days shows no ill effects except for some loss of appetite. During the last twenty-four hours before death, or earlier, the animal becomes stupid and quiet (especially is this the case with cats) and show weakness and uncertainity of movement in

the hinder extremities, "Vincent, "Internal Secretion", p. 140.

3. CONTEMPORARY EXPERIMENTERS.

H. Strehl and O. Weiss in 1901 gave the following table as indicative of their results;-

Species of animal	Duration of survival in hours	Number of animals
Dogs	22-75	7
Dogs	75-138	3
Cats	15-28	15
Cats	28-47	2
Rabbits	8-14	26
Guinea Pigs	4-9	20
Rats	15-19	44
Mice	8-13	10
Hedgehog	14	1
Weasel	21	1
Frogs	22-45	25

They concluded that all animals from which both of the glands have been removed die.

Biedl (4) describes his extirpation according to a special method which he devised;-

"Ich habe noch eine weitere Modification eingeführt, die darin bestand, dass ich die Nebennieren extraperitoneal anging, aber sie in der esten Sitzung nichtentfernte, sondern nur rückwärts dislocirte and sie, mit einen Stiel zur Ernährung in Zusammenhang belassen, zwisch Haut and Musculatur einnante. So dassie lebensfahig, aber vollkommen extraperitoneal erhalten blieben. Erst nach 3 bis 4 Tagen wurden die Nebennieren durch einen kleinen Hautschnitt Blossgelegt und durch einen einzigen Scherenschlag entferent, natürlich ohne dass man dabei mit dem Peritoneum in Beruhrung kam. Exstirpirte ich auf diese Weise bloss die Nebenneire der einen Seite, so Überlebten sammtliche Thiere den Eingriff unbegrenzt lange; entfernte ich die Nebeneieren biederseits-- bie dem beschrienbenen Operations verfahren kann mir niemand entgegenhalten, dass der Eingriff ein Scwerer sei-- gingen Sämmtliche Thiere nach 3 bis 4 Tagen ein. Damit war zunächst der sichere Beweis für die Lebenswichtig Keit der Nebennieren erbracht."

I would offer in criticism that this is not so simple as the author would have us believe. From what is know concerning the relations of the glands, I do not think that they can be dissected out through the lumbar incision, with their blood supply intact, and stitched beneath the skin. Moreover judging from actual dissections made I do not consider that the arteries, are long enough and strong enough to admit of such a stretching. If Biedl had described his operation as fixing the glands at the base of the lumbar incision I would be more inclined to agree with him. Even this would be most difficult in the case of the right side.

I give the results of H. & A. Cristiani (11) as being opposed to those of Harley, Boinet and Weisel, which were quoted above. These brothers report that rats die within twenty-four hours after total extirpation.

In my own work upon rats I have obtained a similiar to that of the Cristiani's. I have employed twenty white rats, and in no case did one survive which had both of the glands removed.

I destroyed the glands by cauterisation, this possessing the advantage over extirpation of controlling the haemorrhage, eliminating ligatures and being quicker.

It would appear that the evidence in regard to the white rats is too confusing to admit of proof as to whether the glands are essential to life or not.

Very conclusive evidence is forthcoming from the experiments upon guinea pigs by A. Velich (34). He states that the total removal of both glands in these animals invariably results in death. He has noticed the marked hypertrophy of one gland and the accessory bodies after the other gland has been removed. Velich also demonstrated the hypertrophy of the accessory bodies alone after both of the glands had been extirpated, but thinks that this is insuffic ent to admit of the life of the animal. In this he disagrees with Stilling.

4.RESULTS OF MY EXTIRPATION EXPERIMENTS.

In my own work, in an effort to destroy all of the medulla I have so damaged the cortex that there was not enough of this for the animal to survive upon. We see that the result would be equivalent to total extirpation. I report the death of twenty dogs, eighteen cats, and two rabbits in which the post-mortem examination showed no other cause of death except that of adrenal insufficiency. In no case was there more than one-eighth of the normal cortical tissue of one gland found. The animals always died within twelve to forty-eight hours.

5. CONCLUSIONS.

Form a consideration of the evidence given, I think that I am justified in drawing the following;

1. The removal of one gland always gives negative results. In fact, if we except a slight loss in weight, there are no pathological signs. There is always a slight hypertrophy of the other gland and perhaps of the accessory bodies. This shows that the negative result is not due to an absence of functional significance, but to the fact that the suppressed function is replaced by the greater activity of the remaining portions.

2. The extirpation of both glands is always followed by death within a few hours, though we must admit a few exceptional cases where survivals are reported. This is not due to the severity of the operation or to secondary causes, because careful controls can be made which develop quite normally. The death occurs solely as a result of the suppression of these organs. This was especially illustrated in the experiments of Biedl, in which the glands were first displaced and stitched under the skin and then after an interval, completely extirpated, this second operation being only a very slight one. Death always followed this within twenty-four hours.

We would state that the adrenals are not only important to life but that they are essential to it.

3. If the adrenals are removed together or in different stages, the result of complete extirpation is always fatal. A difference may be noticed that where they are taken out in stages the survival time may be lengthened. This may be explained by the fact that the accessory tissues have had time to grow, though not to a sufficient extent to admit of the life of the animal.

4. In general, it may be said of those animals which survive after complete extirpation that they have an extra amount of accessory tissue.

5. Parts of the glands may be extirpated without fatal results. The survival depends upon the amount of the tissue that is left. Langois places this minimum amount at one-sixth of the total glandular weigh, Biedl at one-eighth, and my own work would prove to be something more than one-tenth.

B. ON THE RELATIVE IMPORTANCE TO LIFE OF THE MEDULLA AND THE CORTEX.

1. INTRODUCTORY.

It has been proven that the adrenals as homogenous organs are necessary to the life of the animal. Experiments undertaken with the idea of proving this have also thrown out hints that a certain small part of the gland left behind may be sufficient for the animal to survive upon. As to which part of the gland this must be I shall endeavor to prove.

We know that adrenin, which has such specific physiological effects, is to be obtained only from the medulla of the gland. In animals from which the supraranal medulla has been removed it seems likely that death would result from lack of that essence which is elaborated in it. My conclusion seem obvious, then, that it is this part which is essential to life. It has been suggested by some that adrenin maintains the state of "normal tonus" in the body; after the removal of the suprarenal the animal dies because of lack of this.

Strehl and Weiss (30), first workers upon this question, showed that the extirpation of both glands is immediately followed by a considerable fall in the blook-pressure. Their operation was to extirpate one of the glands, and to ligature off the other. This gave, though only in a small minority of cases, a slight fall in the blood-pressure. On the removal of the ligature on the one gland the blood-pressure immediately came back to normal.

Young and Lehmann(37) did not obtain similiar results.

We see that in a way we are justified in assuming that it is the medulla which is essential to life. However, all experimental evidence does not bear this out.

2. RESULTS IN FAVOUR OF CORTEX AS ESSENTIAL PART.

Very considerable evidence is to be derived from a study of the accessory adrenal tissue that is found in animals, thus;-

Stilling (28) demonstrated the compensatory hypertrophy after unilateral extirpation, and observed that it was only the cortex which enlarged, and not the medulla.

Boinet (8), in working with white rats, and extirpating the accessory tissue as well as the glands, observed that the former is composed only of cortical tissue.

Wiessel (36) demonstrated accessory adrenals to be present in fifty per cent of the cases that he examined. THey were always free of all medulla.

Biedl (5) goes so far as to state that the animals which survive total extirpation have sufficient of this accessory cortical tissue to maintain their life.

Another source of information is a study of the compensatory hypertrophy of one gland when the other is removed.

Stilling (29) observed that it is the cortical tissue alone which hypertrophies.

Velich (34) in working with guinea pigs obtained similiar results.

Pettit (23) observed this compensatory hypertrophy in fishes. It was afterwards proven that he was observing only cortical bodies.

The transplantation experiments of Poll (25) gives us still further evidence. He was a very accurate and systematic observer and was the first to make a microscopical examination of the transplanted gland. It is claimed by him ttat in the grefted glands the inner part of the zona fasciculata, zona reticularis, and medulla degenerate within the first week; it becomes necrosed and is finally absorbed. On the other hand, the zona glomerulosaand

the outer part of the zona fasciculata remain only slightly altered. The ultimate result is that we have only cortical cells functioning in this transplanted gland.

"Stilling (29) also transplanted adrenals into the testis and found typical cortical tissue as long as three years after the operations". Vincent, "Internal Secretion", p. 153.

H. & A. Cristiani (11) obtained results which agree in every detail with those of Poll.

One attempt has been made to settle this question, that of the relative importance of the medulla and cortex, by direct experiment. By direct experiment we mean, to destroy either tissue and to observe the result. Biedl (6) in his extirpation results makes the statement that one-eighth of the normal cortex is sufficient to maintain the life of the animal. He describes an experiment in which all of the cortex was removed leaving the medulla intact. Death resulted in every case within twenty-four hours. It seems difficult to understand how

such an operation could be successful when one bears in mind the relations of the glands to the large blood vessels, nerve plexuses, and the relative proportion of the cortex to the medulla as 10:1, Elliott and Tuckett (29).

Biedl (7) in working with Elasmobranch fishes describes how he removed all of the interrenal tissue. The animals always died, with all the symptoms of complete adrenal extirpation.

3. RESULTS IN FAVOR OF MEDULLA AS ESSENTIAL PART.

Vassale (33) found that if the medulla was removed from cats and rabbits, they always died as if the adrnals had been removed intact. He attributes any survivals to the fact that they possess a larger amount of the extra-capsular chromaphil tissue.

Zanfrognini and Ciaccio (38) confirm the results of Vassale.

H. & A. Cristiani (11) in working with rats found that the animals always survived if a sufficient amount of the medullary tissue were left.

Vincent (35) reports that eels survive after the cortical tissue is destroyed. However, Giacomini has since demonstrated the presence of cranial cortical bodies in Teleosts; this may account for the survival of these animals.

Some authorities claim that the compensatory hypertrophy on the part of the abdominal chromaphil body after the rest of the medullary tissue has been extirpated may be taken as evidence that the medulla is of vital importance. For my part in all the cases which I have examined where all, or nearly all, the medulla was destroyed. I have never been able to demonstrate any greater activity on the part of the abdominal chromaphil body.

We see that the preponderance of evidence is in favour of the view that it is the cortex which is the essential part. My experiments constitues an attempt (on a larger scale, I believe, than those of previous observers) to settle this point by direct experiments.

4. TECHNIQUE OF MY EXPERIMENTS.

My plan was to destroy all the medulla, without serious damage to the cortex, and to note the duration of the survival. The first method suggested was to stain the interior of the gland with a sterile five per cent potassium bichromate solution. This causes it to appear "in situ" a rosy-pink colour. A control experiment carried out upon the abdominal chromaphil body proved that this method would be useless; for, though the body stains deeply "in situ" it can be recognised after a survival of ten days. A second staining is necessary before the body can be distinguished. Thus, it would appear that the destruction of the chromaphil tissue can not be caried out by means of potassim bichromate.

The cautery was the method finally used. The glands were exposed from the front. The left was completely extirpated; the lumbar vein crossing the right and ligatured on both sides, the gland carefully dissected free of the peritomeum and the fat, and an effort made to cup out the entire medulla with the cautery. In dogs a more extensive extirpation was carried out, half of the right gland was amputated and the remainder cauterised. The animals were allowed to

survive for three weeks or a month after the final operation. The glandular tissue found at the post-mortem examination was stained with Müller's fluid, and serial sections were cut, in a search of any medulla that might have escaped at the operation.

5. RESULTS.

We have employed 30 dogs, 22 cats and 4 rabbits.

A. 13 dogs, 4 cats, and 2 rabbits.
In these animals we could find no medulla at the post-mortem examination. They died within 12-48 hours. The cortex was extensively damaged; in no case, was there more than 1/6 of the normal cortical tissue left.

B. 10 dogs.
These animals were destroyed after a month and a post-mortem examination showed that more than one half of the medulla had been destroyed.

C. 4 dogs, 6 cats, 1 rabbit.
These animals were destroyed after a month and the examination showed only the slightest trace of medulla.

D. 1 dog, 2 cats.

These animals were destroyed after a month. The serial sections showed that there was absolutely no medulla left.

At present we have 2 dogs, 7 cats, and 1 rabbit, some of which have been operated upon for a second time. They are showing no symptoms.

6. SYMPTOMS.

We were unable to notice any special symptoms in these animals in which the medulla was extensively damaged or even totally removed. In two or three days they quite recovered from the operation and after this advanced quite normally. In four cases we noticed a slight loss in weight, and in two others an increase; the rest showed no change.

7. COMPENSATORY HYPERTROPHY.

An effort was made to demonstrate a compensatory hypertrophy of the accessory chromaphil tissues after the medulla of the adrenal had been extensively damaged or totally removed. Accordingly

the abdominal chromaphil body was stained at each post-mortem and comparison made of the size of this with those of control animals. In no case am I able to state that this body was larger than normal.

8. CONCLUSIONS:-

The entire destruction of the medulla of both glands gives negative results. In fact there are no pathological signs. There is never any compensatory hypertrophy of the accessory chromaphil tissues; this shows that the negative result is probably due to an absence of functional significance of this part of the gland. Animals in which the medulla has been entirely removed are seen to progress quite normally; therefore we would state that the medulla of the adrenal is not essential to the life of the animal.

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