THE EFFECT OF EXTRACTS OF SUPRARENAL CORTEX ON THE BLOOD CALCIUM

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INTRODUCTION.

It has been established beyond doubt that the cortex of the suprarenal has an internal secretion, total removal of which is invariably fatal. The nature of this internal secretion and its influence on the body processes have so far been very slightly elucidated.

As far back as the year 1806 Meckel noted a relationship between the adrenal bodies and the reproductive organs. There is a close resemblance morphologically and histochemically between the cells of the suprarenal cortex and of the interstitial cells of the ovary, and especially those of the corpus luteum. On histological grounds alone, some observers go so far as to speak of the corpus luteum of pregnancy as a temporary cortical adrenal body. Embryologically the cells of the suprarenal cortex are derived from the germinal epithelium, from which the sex glands also take origin. It has been noticed that the suprarenal cortex hyper trophy during ovulation and pregnancy, and as the result of the removal of the gonads; and it has also been stated that sexual vigour is related to the size of the cortex.

But the most striking and suggestive evidence of a relationship between the suprarenal cortex and the gonads is to be obtained from the study of clinical pathology. The occasional occurrence of tumours of the adrenal cortex called cortical hypernephromata is associated with precocious sexual development or reversion to the secondary sexual characters of the opposite kind. The cells of these tumours closely resemble, histologically, normal cortical tissue and may be conceived to function as such, and lead to the excessive formation of the specific internal secretion. Many experimental attempts have been made to correlate the function of the cortex with the gonads, but so far nothing definite has been demonstrated. Most experimental work in this direction has taken the form of feeding suprarenal cortex—or more usually whole suprarenal—and noting if there is any increase in weight of either the testis or ovary. The value of some of these results is to a large extent vitiated by the fact that the preparations used were defatted.

The large amount of experimental work done has so far produced few consistent results. Lewis(1) stated that in doubly adrenalectomised rats the
reproductive functions are apparently normal. R. G. and A. D. Hoskins(2) report hypertrophy of the testes and ovaries in rats fed on commercial desiccated adrenal gland. McKinley and Fisher(3) found that the testes of rats fed on cortex were 21.5 per cent. heavier than the testes of control animals. Kichikawa(4), as the result of ablation and grafting experiments, comes to the conclusion that the suprarenal cortex has a stimulating influence on the apparatus on which the development of the sexual characteristics depends. Jaffe and Marine(5) find moderate or marked hypertrophy of the interstitial cells of the ovary in rabbits as the result of double adrenalectomy, but no specific changes in the male gonads as the result of the same procedure(6). The most illuminating work on this subject so far is a recent contribution by Rogoff and Stewart(7). These observers find that the totally adrenalectomised bitch can survive very much beyond the usual maximum period if the operation is done during the condition of “heat” in the animal. Post-mortem of these animals showed a hypertrophic uterus, the ovaries were somewhat enlarged, and numerous corpora lutea were visible on the surface. A similar effect had previously been found to occur in pregnancy. The authors suggest that the cells in the ovary similar in origin and structure to the adrenal cortex have supplied the hormone necessary for life which was present in the cortex. This means that the hormone of suprarenal cortex and the hormone of the ovarian structure in “heat”—probably the corpus luteum—are similar, perhaps even identical.

This conclusion derives striking confirmation as the result of our researches. We became interested in the subject from an entirely different quarter. We had found(8, 9) that alcoholic extracts of ovary have the effect of lowering the concentration of calcium in the blood in rabbits and human beings. Owing to the well-known relationship between the suprarenal cortex and the ovary, we proceeded to investigate the effect of cortical extracts upon the blood calcium.

METHOD.

We had the initial difficulty of obtaining an extract from the cortex without admixture of medullary tissue. We used bovine suprarenals.

Our method was to freeze the suprarenals as soon as obtained from the abattoirs. One could thus, in most cases, peel the medulla away from the cortex fairly well. This was then minced, and repeatedly extracted with alcohol. The alcoholic filtrates were combined, and ammonia added to precipitate any adrenaline present. It was then filtered, the alcohol evaporated off, and the residue extracted with ether; acetone was added to precipitate lipoids, these being subsequently removed by filtration.

The filtrate was then evaporated to dryness, and the residue dissolved in a small quantity of alcohol. This was then put on to ice, when the cholesterol crystallised out and was removed. The final alcoholic solution was taken to dryness and the oily material obtained was “pure” extract. In appearance it was a light
yellow oil of viscid consistency, easily soluble in alcohol, ether and acetone, and
in all its appearances it resembled the "pure" extract obtained from corpus luteum.

In some cases the first alcoholic extract was merely treated to remove traces
of adrenaline, and was then taken to dryness, and used as such. This we refer to
as the "crude" extract.

We used rabbits for experimental animals, and the "pure" or "crude" extracts
were dissolved in olive oil or 1 per cent. sodium carbonate solution, and injected
either subcutaneously or intraperitoneally. The blood was drawn before injection
and at intervals after injection, and estimated for calcium in the serum by Clark
and Collip's(10) method.

RESULTS.

Table I.
Injection of Extracts of Suprarenal Cortex.

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<td>9.3</td>
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<td>-</td>
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<td>13.2</td>
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<tr>
<td>12</td>
<td>50 gm. &quot;pure&quot; extract E</td>
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<tr>
<td>13</td>
<td>75 &quot;</td>
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Our main results were very similar to those we obtained with extracts of ovary.
As we have treated the subject of the mode of action of the ovarian hormone in
a previous paper (8) very fully, we do not intend presenting here a large number
of results. The results shown in Table I are characteristic of our experiments,
and the other details of its action we will describe without giving more protocols.
 Altogether about fifty rabbits were injected with the extracts.

The blood calcium was found to drop after injection in a large percentage of
the rabbits. The amount of the drop was in the most marked cases 30–35 per cent.
of the original, and occurred usually at the end of 24 hours, but was sometimes
earlier, and at other times occurred only after 48 hours. The blood calcium
returned to normal usually within 72 hours. The same effect occurred on sub-
cutaneous and intraperitoneal injections. The effect was the same in both sexes.
The rabbits appeared normal in all respects.

As controls we employed rabbits in which we injected equivalent amounts of
olive oil, cholesterol or sodium carbonate solution and also alcoholic extracts of
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bovine muscle, pancreas, spleen, kidney and brain prepared in the same manner as the suprarenal cortex extracts. These rabbits were kept along with the other experimental animals, and bled at the same intervals, without any significant change of the blood calcium values. A more complete account of some of these controls is to be found in our previous paper (8).

DISCUSSION.

Our experiments show for the first time a definite measurable relationship between the suprarenal cortex and the gonads with regard to a certain phase of metabolism. The cortex appears to contain the same calcium-reducing internal secretion as the ovary, and in about the same concentration, and the mode of action of the two seems indistinguishable. What the exact significance of this finding is, it is difficult at the moment to interpret, but it will certainly explain many phenomena.

Our experiments were actually performed nearly two years ago, and since then evidence of the relation between the internal secretion of the suprarenal cortex and calcium metabolism has been forthcoming from other sources.

Rogoff and Stewart (11) found that when totally adrenalectomised dogs begin to exhibit the train of serious symptoms terminating in death, after the preliminary good health maintained subsequent to the operation, then at the same time there occurred in most cases a decided rise in the blood calcium, rising from the normal of about 11 to as high as 17 mg. per 100 c.c. of serum. These results are such as we would expect from the consideration of the effect of the injection of cortical extracts. Taylor and Caven (12), in a preliminary communication, note that they found that removal of both adrenals in cats and dogs produced a rise in blood calcium in three to five hours, the rise being from 10 to 40 per cent. Extracts prepared from the cortex (method not given) depressed the serum calcium in rabbits from 15 to 30 per cent. These confirm our results. In addition they find that the action of the suprarenal cortex only affects the calcium level when there is some parathyroid tissue present—a conclusion we had come to in our work on the ovary, when we stated we could never produce tetany by increasing the dose of the ovary extract enormously. From various considerations we came to the conclusion that the calcium-reducing hormone acts by antagonising the parathyroid hormone.

There now arises the question whether the hormone obtained from the suprarenal cortex that lowers the blood calcium is identical with that present in the ovary and the corpus luteum. We have not performed any elaborate physicochemical investigations of our extracts, but our own impression is that they are extremely alike. It will be interesting to determine whether extracts of the suprarenal cortex prepared according to our method will produce oestrous changes in the spayed rat or mouse. Such an investigation may throw light on the question whether the calcium-reducing property of ovarian extract is a function of the
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Oestrous-producing hormone, or whether we are dealing with two separate internal secretions.

At any rate our investigation shows that there is definitely a metabolic relationship between the suprarenal cortex and the ovary, and there is no doubt that it will help to clarify many of the phenomena associated with parturition, and possibly explain the extraordinary sex changes associated with tumours of the suprarenal cortex.

SUMMARY.

1. An extract has been prepared from the suprarenal cortex, which, when injected into rabbits, lowers the blood calcium to the extent of about 30 per cent.; the maximum fall occurs after 24 hours, and returns to normal in about 48 hours.

2. The extract prepared from the suprarenal cortex resembles that obtained from ovary and corpus luteum, both in physical characteristics, and in the production of a typical response on the part of the blood calcium.

3. It would appear that the hormone of the suprarenal cortex that is capable of lowering the blood calcium is very similar and possibly identical with the hormone of the ovary, having the same function.

4. A definite relationship has been established between the suprarenal cortex and the ovary, justifying the long-suspected connection between the two glands.

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REFERENCES.