CXIX. THE SEXUAL GLANDS AND METABOLISM.

IV. THE INFLUENCE OF INJECTIONS OF EMULSIONS OF TESTES AND PROSTATE AND OF INSULIN-LIKE TESTICULAR EXTRACTS UPON THE NITROGEN METABOLISM OF NORMAL, CASTRATED AND THYROIDECTOMISED RABBITS.

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I. HISTORICAL.

CASTRATION produces a fall in the nitrogen metabolism of most dogs and rabbits [Korenchevsky, 1925, 1]. Dog's testes contain specific hormones which probably prevail when injected in the form of testicular emulsion [Korenchevsky, 1925, 2]. This is indicated by an increase in the nitrogen metabolism of most dogs after these injections. Thyroidectomy in dogs does not change this effect. It seems that in dogs the sexual hormones do not produce their influence upon nitrogen metabolism by means of the thyroid or at any rate not exclusively. On the other hand, Korenchevsky and Carr [1925] found that homologous testis emulsion when injected subcutaneously into rabbits slightly decreased the nitrogen metabolism during the period of injections and in most cases during the succeeding 5-9 days. This effect of testis emulsion cannot, however, be considered to be a specific one because of the similar effect of kidney emulsion.

An emulsion of prostate, injected alone or in combination with testis, increased the nitrogen metabolism up to 11 %. The rise in N output was manifested more particularly during the 2 or 3 days following the period of injections.

The diminished N metabolism after the injection of testis emulsion in the rabbit was contrary to expectation because castration also produces a fall in the nitrogen metabolism [Korenchevsky, 1925, 1]. Therefore we were inclined to attribute these contradictory results chiefly to the possible presence in the rabbit's testis of two different principles, one increasing, the other decreasing nitrogen metabolism, the latter prevailing when an emulsion of this organ is injected. Ashby [1923], Baker, Dickens and Dodds [1924],

Ivy and Fisher [1924] and Best, Smith and Scott [1924] have found that various tissues, including kidney, contain an insulin-like substance. And according to Fitz, Murphy and Grant [1922], Wilder, Boothby, Barborka, Kitchen and Adams [1922], MacLeod and Allan [1923] and Kudrjavzeva [1925] injections of insulin lower the nitrogen metabolism. Therefore, if testes contain an insulin-like factor, this latter substance may partly be the cause of the decreased nitrogen metabolism.

The experiments to which we shall refer in this paper seem to justify this theory.

II. THE PRESENT INVESTIGATION.

Technique.

Twenty-three experiments were performed on 12 rabbits, of which 4 were castrated (Nos. 14, 22, 26, 33), 4 thyroidectomised (Nos. 24, 31, 38, 39), 3 both thyroidectomised and castrated (Nos. 23, 17, 40) and 1 normal (No. 41). The technique of the metabolism experiments, the preparation of the emulsions of prostate and testis and the amounts injected are the same as those described in a previous paper [Korenchevsky and Carr, 1925].

Mr F. H. Carr at the laboratories of the British Drug Houses isolated insulin-like substances from bull's testes and kindly supplied us with the amount necessary for our experiments—we wish to thank him and his firm for this as well as for the following data concerning the method of purification and the influence of these substances upon the blood-sugar of rabbits, the latter being determined by Dr S. W. Underhill.

The method of isolation briefly consisted in the precipitation of alcoholic extracts of bull's testes at different p_H values, namely, p_H 6·8 (testicular extract A), p_H 5·0 (testicular extract B) and p_H 4·0 (testicular extract C). These three substances were converted to hydrochlorides by Dudley's method. They reduced the blood-sugar content of rabbits as follows:

Testicular extract A.	2·5	mg. per kg.	reduced the blood-sugar to	55	mg. per 100 cc.		
	4·0	"	"	74	"	"	
Testicular extract B.	0·15	"	"	44	"	"	
	0·25	"	"	50	"	"	
	0·4	"	"	51	"	"	
Testicular extract C.	2·0	"	"	45	"	"	
	3·0	"	"	54	"	"	

For our experiments these three fractions were each dissolved in sterile distilled water and injected subcutaneously in amounts varying between 0·8 mg.–2·3 mg. per diem and per kg. of the rabbit's weight. The amounts injected per diem and kg. are given in the tables. Each experiment was divided into four periods, namely, the first control period of 3 days before the injections, the period of injections lasting 3 days, followed by two or three control periods, each of which usually lasted 3 or sometimes one of them only 2 days. When the doses were increased and we feared convulsions might follow, the injection period only lasted for 1 day. For this same reason in

Exps. 2, 7, 12, 15 and 16 the rabbits were injected with small doses (about 0.8 mg. per kg.) for 3 days. Five days after the injection period, when the nitrogen metabolism of the thyroidectomised animals was still below normal, another larger injection was given once only.

In normal or castrated animals fractions A, B and C were injected in the same or larger amounts.

In order not to increase the amount of tabular matter, firstly, we do not include the experiments on testicular extract A, because its activity was small, nor the experiments on the injections of a mixture of A, B and C extracts, because the results obtained were nearly identical with those with B extract. Secondly, though the nitrogen intake in the food and output in the urine and faeces were estimated carefully as in our previous work, they are not included in the tables. The daily intake of nitrogen was always the same during a whole experiment. It only varied slightly in different experiments, because the cabbage could be stored for the length of one experiment only (about 18 days), but not for all the experiments on the same animal [for further details see Korenchevsky and Carr, 1925, pp. 77, 78; Korenchevsky, 1925, 3].

Description of the Experiment.

The actual figures and details of the experiments are given in Tables I and II and the results obtained are summarised in Tables III and IV. In the latter the figures show the average percentage change above (+) or below (−) normal in the urinary nitrogen excretion and in the urinary flow during the period of injections and the two or three following control periods, compared with that of the same animal during the first control period before the injections. In Tables III and IV the average percentage changes in thyroidectomised animals are compared with those in normal or castrated animals with thyroids. The average figures of the urinary nitrogen and flow of the latter animals were taken from experiments published previously [Korenchevsky and Carr, 1925]. As was mentioned above, the experimental technique was exactly the same in both.

Injections of Testis Emulsion.

The details of these experiments on rabbits 23 and 24 are given in Table I (Exps. 1 and 3) and Table II (Exp. 10). Before the period of injections in Exp. 1 the nitrogen balance was positive, but was negative in this period in Exps. 3 and 10. The results of all three experiments were almost identical, namely, a quite definite decrease in the nitrogen excreted in the urine (15.5, 14.5 and 7.2 % respectively below normal) and an increase in the nitrogen balance. This was always most pronounced, and in two experiments was only present in the control period following the injections.

A comparison of the results obtained on animals with thyroids and on those without thyroids (see Table III) shows that the injection of testis

Table I. *The influence of subcutaneous injections of insulin-like extracts from testis and of emulsions of testis and of prostate upon the nitrogen metabolism of rabbits.*

No. of experiment and rabbit	No. of period	Weight of rabbit g.	Volume of urine excreted cc.	Nitrogen in urine g.	Balance of nitrogen g.	Remarks
<i>Exp. 1</i>						
Rabbit 23 (thy-roidectomised and castrated)	I	3575	448	9.43	+0.11	I control period
	II	3577	462	9.57	-0.13	Injection of testis emulsion
	III	3605	375	8.27	+1.17	II control period
	IV	3640	348	8.81	+0.63	III control period
	V	3655	504	8.69	+0.78	IV control period
<i>Exp. 2</i>						
Rabbit 23	VI	3490	651	8.07	-1.56	I control period
	VII	3485	628	7.56	-1.05	Injection of 0.9 mg. testis extract C
	VIII	3480	571	7.60	-1.09	II control period
	IX	3480	562	7.48	-0.97	III control period
	X	3500	518	7.17	-0.66	Injection of 1.7 mg. testis extract C
	XI	3475	777	7.83	-1.32	IV control period
<i>Exp. 3</i>						
Rabbit 23	XII	3420	611	7.58	-1.11	I control period
	XIII	3403	565	7.85	-1.38	Injection of testis emulsion
	XIV	3420	420	6.48	-0.01	II control period
	XV	3420	502	6.93	-0.46	III control period
<i>Exp. 4</i>						
Rabbit 38 (thy-roidectomised)	I	2695	418	6.50	-0.52	I control period
	II	2695	385	6.72	-0.74	Injection of prostate and testis emulsion
	III	2685	371	6.51	-0.53	II control period
	IV	2680	373	6.72	-0.74	IV control period
<i>Exp. 5</i>						
Rabbit 40 (thy-roidectomised and castrated)	I	2560	424	6.25	-0.46	I control period
	II	2565	434	6.43	-0.64	Injection of prostate emulsion
	III	2545	485	6.24	-0.45	II control period
	IV	2545	428	6.14	-0.35	III control period
<i>Exp. 6</i>						
Rabbit 17 (thy-roidectomised and castrated)	I	2590	488	8.71	-0.54	I control period
	II	2627	286	7.98	+0.19	Injection of emulsion of prostate and testis
	III	2620	518	8.23	-0.06	II control period
	IV	2620	441	8.57	-0.40	III control period
	V	2595	434	8.56	-0.39	IV control period
<i>Exp. 7</i>						
Rabbit 17	VI	2580	390	7.36	-0.14	I control period
	VII	2550	462	7.34	-0.12	Injection of 0.8 mg. of testis extract B
	VIII	2565	329	6.99	+0.23	II control period
	IX	2560	392	6.93	+0.29	III control period
	X	2520	616	6.92	+0.30	Injection of 1 mg. of testis extract B
	XI	2545	273	6.16	+1.06	IV control period
<i>Exp. 8</i>						
Rabbit 17	XII	2550	401	7.90	-0.15	I control period
	XIII	2580	380	7.80	-0.05	Injection of emulsion of prostate and testis
	XIV	2585	343	7.57	+0.18	II control period
	XV	2565	406	7.70	+0.05	III control period

TE. In this and the following tables figures showing N intake and N content of faeces are omitted for brevity's sake. The figures are calculated for 1 week so as to be comparable. The figures for insulin-like extracts represent the amount injected per diem and kg.

Table II. *The influence of subcutaneous injections of insulin-like extracts from testis and of emulsions of prostate and of testis upon the nitrogen metabolism of rabbits.*

No. of experiment and of rabbit	No. of period	Weight of rabbit g.	Volume of urine excreted cc.	Nitrogen in urine g.	Balance of nitrogen g.	Remarks
<i>Exp. 9</i>						
Rabbit 24 (thy- roidectomised)	I	3185	530	8.49	+0.62	I control period
	II	3215	560	8.37	+0.74	Injection of prostate emulsion
	III	3168	601	8.52	+0.59	II control period
	IV	3195	478	8.71	+0.40	III control period
	V	3275	411	8.36	+0.75	IV control period
<i>Exp. 10</i>						
Rabbit 24	XII	3495	527	9.32	-0.92	I control period
	XIII	3485	548	8.92	-0.52	Injection of testis emulsion
	XIV	3495	462	8.65	-0.25	II control period
	XV	3485	586	8.82	-0.42	III control period
<i>Exp. 11</i>						
Rabbit 31 (thy- roidectomised)	I	2555	537	7.65	-0.29	I control period
	II b	2567	392	5.70	+1.66	Injection of 1.4 mg. testis extract B
	V	2565	553	7.51	-0.15	IV control period
<i>Exp. 12</i>						
Rabbit 31	VI	2542	504	7.25	-1.93	I control period
	VII	2505	537	7.25	-1.93	Injection of 0.8 mg. testis extract B
	VIII	2520	392	6.36	-1.04	II control period
	IX	2545	436	6.28	-0.96	III control period
	X	2550	392	5.73	-0.41	Injection of 1.0 mg. testis extract B
<i>Exp. 13</i>						
Rabbit 31	XII	2408	488	7.33	-1.41	I control period
	XIII	2370	567	7.34	-1.42	Injection of prostate emulsion
	XIV	2330	553	7.25	-1.33	II control period
	XV	2320	495	7.15	-1.23	III control period
<i>Exp. 14</i>						
Rabbit 33 (castrated)	I	2570	586	8.72	-0.18	I control period
	II	2555	525	8.48	+0.06	Injection of 1.4 mg. testis extract C
	III	2560	478	9.07	-0.53	II control period
	IV	2580	455	8.76	-0.22	III control period
	V	2565	436	8.41	+0.13	IV control period
<i>Exp. 15</i>						
Rabbit 33	VI	2627	495	8.28	-0.52	I control period
	VII	2620	490	7.80	-0.04	Injection of 1.2 mg. testis extract C
	VIII	2640	403	7.91	-0.15	II control period
	IX	2640	488	8.00	-0.24	III control period
	X	2650	392	8.06	-0.30	Injection of 2.3 mg. testis extract C
	XI	2645	455	7.80	-0.04	IV control period
<i>Exp. 16</i>						
Rabbit 14 (castrated)	I	3285	455	8.67	+0.39	I control period
	II	3295	420	8.40	+0.66	Injection of 0.9 mg. testis extract B
	III	3310	378	8.52	+0.54	II control period
	IV	3310	413	8.30	+0.76	III control period
	V	3300	546	8.30	+0.76	Injection of 1.3 mg. testis extract B
	VI	3305	378	8.19	+0.87	IV control period
<i>Exp. 17</i>						
Rabbit 26 (castrated)	I	2197	432	7.10	0	I control period
	II	2135	487	7.11	-0.01	Injection of 1.3 mg. testis extract B
	III	2160	348	7.66	-0.56	II control period
	IV	2160	387	7.10	0	III control period
	V	2165	395	6.98	+0.12	IV control period
<i>Exp. 18</i>						
Rabbit 41 (normal)	I	2880	443	9.04	-0.23	I control period
	II	2895	364	8.29	+0.52	Injection of 1.5 mg. testis extract B
	III	2890	280	9.03	-0.22	II control period

Table III. *Average percentage change from the normal in the N output in the urine of rabbits after injection of insulin-like extracts from testis and of different emulsions.*

Injection	Number of experiments averaged	Thyroid present (+) or removed (-)	Experimental periods			
			Injection period 3 days	II control period 2 days	III control period 3 days	IV control period 2 days
Kidney emulsion	3	+	- 4.4	- 4.9	- 4.8	.
Testis emulsion	4	+	- 4.6	- 2.5	- 2.4	.
	3	-	+ 0.2	- 12.4	- 7.1	- 7.9
Prostate emulsion	4	+	+ 3.1	+ 9.0	+ 1.5	+ 3.3
	3	-	+ 0.5	- 0.2	- 0.5	- 1.6
Prostate and testis emulsion	5	+	+ 0.5	+ 9.2	+ 3.3	+ 1.3
	3	-	- 2.1	- 3.3	- 0.3	- 1.7
Testis insulin B per diem and kg.						
0.9 mg.	1	+	- 3.2	- 1.8	- 4.3	.
0.8	2	-	0	- 8.6	- 0.7	.
1.3-1.5	3	+	- 4.2	- 0.8	.	.
1-1.4	3	-	- 17.5	- 26.9	.	.
Testis insulin C per diem and kg.						
1.2-2.3 mg.	3	+	- 3.9	- 2.0	- 1.7	.
0.9-1.7	2	-	- 8.8	- 4.7	- 7.4	.

Table IV. *Average percentage change from the normal in urinary flow of rabbits after injection of insulin-like extracts from testis and of different emulsions.*

Injection	Thyroid present (+) or removed (-)	Injection period	II control period	III control period
Kidney emulsion	+	- 5.5	- 4.6	+ 5.0
Testis emulsion	+	- 8.8	- 15.8	- 12.0
	-	- 0.2	- 19.9	- 9.6
Prostate emulsion	+	- 5.1	- 0.1	- 8.6
	-	+ 8.1	+ 13.7	- 2.4
Prostate and testis emulsion	+	- 2.4	- 12.7	- 13.3
	-	- 18.2	- 6.6	- 6.4
Testis insulin B	+	+ 1.8	- 22.5	- 9.8
	-	+ 1.5	- 17.9	- 6.8
Testis insulin C	+	- 10.4	- 15.0	- 12.4
	-	- 12.0	- 15.9	- 13.7

emulsion decreased the nitrogen metabolism of thyroidectomised rabbits much more than that of normal or castrated animals.

Urinary flow was also decreased in the period following the injections, but, as the corresponding figures in Table IV show, there was no essential difference in this respect between the animals with and those without thyroids. This decrease in flow is incapable of interpretation, because we have not measured the water expired nor the water content of the faeces. Moreover, only in one experiment (No. 1) of the three was there an increase in weight. Therefore, there are no definite indications that the water is retained in the organism. The percentage of nitrogen excreted in the dried faeces was slightly increased in two experiments (Nos. 3 and 10) and slightly decreased in one (No. 1).

Injections of Prostate Emulsion.

The details of these experiments on rabbits Nos. 24, 31 and 40 are given in Table I (Exp. 5) and Table II (Exps. 9 and 13). These figures and a comparison of the results obtained on rabbits with thyroids with those on rabbits without thyroids show that the increase in nitrogen metabolism produced by the injection of prostate emulsion in animals with thyroids was not observed in the thyroidectomised animals.

Table IV shows that the excretion of urine during the injections of prostate emulsion and the succeeding period was increased in all thyroidectomised animals, whereas that of rabbits with thyroids was on an average slightly decreased.

There were no constant changes in the percentage of nitrogen excreted in the faeces as a result of the prostate injections.

Injections of a Mixed Emulsion of Testes and Prostate.

The details of these experiments on rabbits Nos. 17 and 38 are shown in Table I (Exps. 4, 6 and 8). The results of these experiments agree well with those of the two previous groups as is shown clearly in Table III.

The increase in nitrogen metabolism produced in rabbits with thyroids after the injection of prostate alone or of prostate and testis simultaneously was not found in the thyroidectomised rabbits. Moreover, when an emulsion of both prostate and testis was injected into the latter animals, on an average, a slight decrease was observed in the nitrogen metabolism, *i.e.* a change typical of testicular emulsion.

Therefore these groups of experiments show, firstly, that in order to produce an increase in the nitrogen metabolism after injection of prostate emulsion the thyroid gland must be present; secondly, that in thyroidectomised animals, when an emulsion of both testis and prostate is injected, the influence of the former gland prevails. The latter result is also corroborated by the decreased urinary flow in Exps. 4, 6 and 8, *i.e.* a change in the excretion of urine typical of the influence of testicular and not of prostate emulsion was observed. No definite or constant change was obtained in the percentage of nitrogen excreted in the faeces.

A slight increase in weight of rabbit No. 17 was observed during the injection period and the following control periods, but rabbit No. 38 slightly decreased in weight in the control periods following the injections.

Injections of Insulin-like Extracts (B and C) of Bull's Testes.

Extract B was injected into rabbits Nos. 14, 17, 26, 31 and 41 and details are given in Table I (Exp. 7) and Table II (Exps. 11, 12, 16, 17 and 18). Extract C was injected into rabbits 23 and 33 (see Table I (Exp. 2) and Table II (Exps. 14 and 15)). The difference between the influence produced by extracts B and C upon nitrogen metabolism was only of a quantitative nature and was

due to the presence of a greater amount of testicular insulin in extract B than in C (see the influence of these extracts upon the blood-sugar of rabbits mentioned above). When 0.8–1.5 mg. of extract B or 1.2–2.3 mg. of extract C per kg. and diem were injected subcutaneously into normal or castrated rabbits, in nearly all cases, only a slight fall was produced in the nitrogen metabolism. Similar or even smaller doses injected into thyroidectomised rabbits produced a much more pronounced decrease in the nitrogen metabolism (see Table III). This effect lasted and, in some cases, was only present or most pronounced in the control periods following the injections.

The percentage of nitrogen in the faeces was slightly increased in about half of the experiments and was decreased or not altered in the other half.

Urinary flow was quite definitely decreased in all cases during the control periods (5–8 days) following the injections, but during the injection period itself it was increased in five cases (36 %) and decreased in nine cases (64 %).

The weights of the animals under the influence of the injections changed a little in both directions; for example, during the control period immediately following the injections half increased and half decreased in weight. Therefore it was quite impossible to establish any relationship between the change in weight and the change in urinary flow, which, as we mentioned above, was diminished in all animals during this same period.

DISCUSSION.

The presence or absence of the thyroid gland seems to be of importance for the changes in the nitrogen metabolism produced in rabbits by emulsions or extracts of testis and prostate glands. Testis emulsion and insulin-like substances obtained from the testis produced only a slight fall in the nitrogen metabolism of normal or castrated animals, probably because the thyroid hormones counteract this influence. In a previous paper [Korenchevsky, 1914] it was shown definitely that the thyroid gland is a great stimulant to nitrogen metabolism. Therefore it is quite reasonable to suppose that, as this effect was lacking in the thyroidectomised animals, the fall in the nitrogen metabolism after injections of testis emulsion and testicular insulin-like substances would be much greater than in the animals with thyroids. These observations agree well with the experiments of Bodansky [1923], Houssay and Busso [1924] and Ducheneau [1924], who found that toxic effects and lowering of blood-sugar produced by insulin were more pronounced in thyroidectomised than in normal animals.

The similarity between the influence of testis emulsion and that of insulin upon nitrogen metabolism and to some extent upon the excretion of urine suggests that the fall in nitrogen metabolism and urinary flow obtained in rabbits after the injection of testis emulsion might be partly due to the presence of insulin-like substances in the testes. The same explanation might apply to the decrease in the nitrogen metabolism of rabbits after the injection of kidney emulsion [Korenchevsky and Carr, 1925].

Experiments with prostate emulsion injected into normal and thyroidectomised rabbits have shown that the thyroid gland must be present in order to obtain an increase in the nitrogen metabolism: in thyroidectomised rabbits an emulsion of prostate alone produced practically no change in the nitrogen metabolism, whereas an emulsion of both prostate and testis usually decreased the nitrogen metabolism, although to a less degree than when an emulsion of testis alone was injected.

It seems probable, therefore, that the prostate emulsion produced its influence upon the nitrogen metabolism of rabbits indirectly through the thyroid gland. This mechanism is not found to work with the testicular emulsion, which, as the experiments on dogs show [Korenchevsky, 1925, 2], increases the nitrogen metabolism of thyroidectomised as well as that of normal and castrated animals.

Unfortunately it is not possible from our experiments to explain the mechanism which decreases urinary flow after the injections of testis emulsion and testicular insulin-like substances.

In our experiments thyroidectomy did not influence the changes in the excretion of urine produced by testis emulsion or insulin-like substances, but it did affect the change in flow after injections of prostate emulsion.

CONCLUSIONS.

1. An homologous emulsion of testis decreased the nitrogen metabolism of thyroidectomised rabbits much more than that of normal or castrated animals.

2. This emulsion also decreased urinary flow to about the same degree in rabbits both with and without thyroid glands.

3. The insulin-like substances isolated from testes and injected into thyroidectomised rabbits also produced a more pronounced decrease in nitrogen metabolism than in rabbits with thyroids.

4. These substances decreased the excretion of urine in both thyroidectomised and non-thyroidectomised animals during the periods following the period of injection, as did testicular emulsion. During the period of injection itself the flow of urine increased in about one-third of the experiments and decreased in the other two-thirds.

5. Thyroid hormones appear to counterbalance the depressing influence on N metabolism of rabbits produced by an emulsion of rabbit's testis or of testicular insulin-like substances.

6. The similarity between the effects of testicular emulsion and of the insulin-like substances extracted from testis suggests that in the former case the fall in nitrogen metabolism, and possibly in urinary flow, is in part due to the presence of insulin-like substances in testes.

7. The same explanation might apply to the decrease in the nitrogen metabolism of rabbits after an injection of kidney emulsion since insulin-like substances have also been isolated from kidney.

8. An homologous emulsion of prostate alone produced practically no change in the nitrogen metabolism of thyroidectomised rabbits, whereas in that of rabbits with thyroid glands a definite increase was observed.

9. This latter increase was also absent when an homologous emulsion of both prostate and testis was injected into thyroidectomised rabbits; instead, on an average, a slight decrease was observed, indicating the predominance of the testicular part of this mixed emulsion.

10. Prostate emulsion appears to increase nitrogen metabolism of rabbits by stimulating the activity of the thyroid gland.

11. Prostate emulsion increased the flow of urine in the thyroidectomised rabbits, whereas, on an average, the excretion of urine was decreased in rabbits with thyroid glands.

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