77. CORRELATION BETWEEN SEX HORMONES, THYROID HORMONES AND DESOXYCORTICOSTERONE AS JUDGED BY THEIR EFFECTS ON THE WEIGHTS OF ORGANS OF GONADECTOMIZED RATS

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(Received 31 May 1941)

THAT there is a correlation between the endocrine secretions of the adrenal, thyroid and sex glands has repeatedly been suggested in the literature on indirect evidence [see survey of literature, Cramer, 1928; Harington, 1933; Grollman, 1936; Means, 1937; Crotti, 1938]. At the same time, the adrenal, thyroid and sex glands are considered to play some part in a manifold mechanism responsible for the maintenance of physical and mental vigour of the organism.

Therefore an investigation of the interrelation of the hormones secreted by these glands is desirable not only for theoretical reasons, but also for possible practical purposes, since these hormones are already extensively used, although not always on sufficiently scientific grounds, in the treatment of different pathological conditions.

The effect of these hormones, administered separately, on the weights of some organs has been investigated extensively in the case of sex and thyroid hormones, but very little in the case of desoxycorticosterone. In order to avoid repetition, a brief survey of this literature will be given for each hormone in the paragraphs dealing with the respective hormones. As far as we know, the correlative changes in weight and structure of organs produced by these three groups of hormones, sex, thyroid, and corticoadrenal, when administered simultaneously, have not been studied.

In order to elucidate this problem, we undertook a number of experiments, some of which are still in progress. In this paper we shall include only some of the results of the first series of experiments, namely, changes in the weights of the organs. The results of their histological examination will be published elsewhere.

Technique

For the experiments 168 rats were used, 86 males and 82 females. Ten rats were kept as normal controls, and all the remaining animals were gonadectomized when 22-24 days old. The final average age of the rats varied from 167 to 207 days. The distribution of the rats into the different groups, their number in each group, the final body weight and the weights of those organs which were changed in at least some of the groups are given in Tables 1 and 2. All animals were killed by bleeding.

¹ Dr Korenchevsky desires to express to Oxford University, to Prof. E. S. Goodrich and to Prof. J. A. Gunn his own and the Lister Institute's gratitude for the kind hospitality extended to him and his co-workers in the Department of Zoology and Comparative Anatomy and the Nuffield Institute for Medical Research.

Table 1. *The effects of male, oestrogenic and thyroid hormones and desoxycorticosterone, administered alone or in combination, on actual weights of organs of castrated rats*

	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV
	Castrated rats treated with hormones														
	Control rats			Thyroid hormones			Testosterone propionate			Androsterone			Desoxycorticosterone acetate		
	Normal			Small dose			Alone			Small dose			Small dose		
Seminal vesicles (mg.)	1049	13	13	15	1298	1299	1052	61	38	51	14	12	17	80	96
Prostate (mg.)	1394	60	61	67	1382	1133	1217	188	169	185	72	62	62	105	122
Penis (mg.)	357	84	80	70	348	353	336	183	157	150	75	91	63	79	77
Preputial glands (mg.)	95	30	34	31	108	114	99	66	68	73	30	36	38	40	42
Adrenals (mg.)	54	58	58	93	59	49	74	47	47	70	49	53	87	70	88
Hypophysis (mg.)	13.1	15.9	14.2	15.1	14.6	13.4	13.6	13.2	14.4	14.3	16.1	18.3	15.4	41.5	47.7
Thymus (mg.)	167	224	222	111	96	114	117	185	220	118	232	266	122	132	156
Liver (g.)	11.28	8.65	8.86	10.58	10.24	10.17	10.63	9.55	9.73	9.87	9.44	11.73	10.90	8.76	11.09
Kidneys (g.)	2.24	1.66	1.61	2.37	2.03	2.01	2.79	1.83	1.91	2.34	1.90	2.27	2.87	1.82	2.47
Spleen (mg.)	645	848	807	690	738	836	739	687	889	658	702	1324	709	733	885
Heart (mg.)	1101	943	982	1398	1084	1126	1419	1043	1118	1290	999	1270	1437	901	1070
Retropitoneal fat (g.)	7.3	9.5	8.3	1.7	7.1	9.6	2.2	11.8	10.9	1.1	10.8	11.3	1.1	11.1	7.7
Final body weight (g.)	334	293	272	258	313	319	287	324	313	248	306	350	254	257	277
No. of rats in group	4	12	8	3	9	7	3	7	6	3	7	5	2	5	5

Note. In both tables, all the 'small dose' groups belong to the first experiment, the 'large dose' groups to the second experiment, and they should be compared accordingly.

Table 2. *The effects of male, oestrogenic and thyroid hormones, administered alone or in combination, on actual weights of organs of ovariectomized rats*

	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
	Ovariectomized rats treated with hormones												
	Control rats			Thyroid hormones		Androsterone		Oestradiol B.B. 0.015 mg.			Oestradiol B.B. 0.015 mg.		
	Normal	Ovariecto- mized	Small, dose	Large dose	Alone	Small dose	Large dose	Alone	+Thyroid hormones small dose	+ Andro- sterone + thyroid hormones small dose	Alone	+Thyroid hormones large dose	+ Andro- sterone + thyroid hormones large dose
Uterus (mg.)	409	31	39	31	36	40	28	191	220	240	207	238	368
Vagina (mg.)	292	160	187	178	236	224	234	273	304	333	255	307	365
Preputial glands (mg.)	74	49	53	52	131	116	161	48	44	323	49	49	212
Adrenals (mg.)	63	62	63	103	51	52	85	55	84	77	98	166	149
Hypophysis (mg.)	15.1	14.5	14.7	13.4	16.1	13.8	14.5	13.8	15.8	15.4	20.2	20.5	18.8
Thymus (mg.)	136	184	228	192	194	170	137	125	158	133	167	176	152
Liver (g.)	6.66	7.22	7.94	9.53	9.08	9.44	10.75	5.97	7.27	8.21	9.03	13.20	11.70
Kidneys (g.)	1.58	1.53	1.67	2.41	1.75	1.81	2.44	1.34	1.69	1.84	1.79	2.98	3.05
Spleen (mg.)	479	838	788	838	595	783	1564	480	797	978	581	1053	906
Heart (g.)	795	828	853	1158	941	1055	1345	783	907	984	921	1383	1247
Abdominal fat (g.)	17.3	10.4	12.4	0.5	12.8	15.7	1.0	12.0	9.8	17.0	9.0	1.0	2.3
Final body weight (g.)	218	256	262	213	289	288	247	220	223	262	227	233	247
No. of rats in group	6	11	10	3	9	6	3	5	5	6	3	3	3

Only those hormones which are naturally present in the organism were used (administered, however, mostly as esters). The following hormones were given, in the doses indicated per week: in experiments on males—androsterone 4.5 mg., testosterone propionate 0.750 mg. and oestradiol 3-benzoate-17 α -butyrate 0.09 mg. (abbreviated in the paper to 'oestradiol B.B. '); in experiments on females—androsterone 4.5 mg., oestradiol B.B. 0.015 mg. In one experiment (Table 2, cols. VIII–X) this oestrogen was injected only for the first 3 weeks; in the second experiment (cols. XI–XIII) for the first 3 weeks, and also during 2 weeks towards the end of the experiment.

Thyroxine, thyroid powder and desoxycorticosterone were administered to both sexes; the thyroid powder was given by pipette in gum acacia suspension sweetened with honey. The groups receiving a 'small dose' of thyroid hormones were given 30–40 mg. of thyroid powder (Parke, Davis and Co.) three times weekly; the duration of this experiment was 54–58 days. The groups receiving the 'large dose' were fed with 40 mg. three times weekly for the first 3 weeks, 80 mg. three times weekly for the next 6 weeks, and 80 mg. five or six times weekly for the last 2 weeks; this group also received during the last 3 weeks of the experiment 1 mg. injected subcutaneously one to three times weekly (total 9 mg. per rat) of thyroxine sodium (British Drug Houses). The variation in the dose of thyroid hormones was dependent upon the loss in weight and appetite, in order not to impair too much the general condition of the rats. The duration of the 'large dose' experiment was 76 days.

The rats received desoxycorticosterone in the form of two subcutaneously implanted crystalline pellets, one of acetate (50 mg.) and the other of pure hormone (25 mg.). The group of rats receiving the large dose of thyroid received also in addition to the two implanted pellets of desoxycorticosterone, subcutaneous injections of 2–4 mg. weekly of desoxycorticosterone acetate in oil. No difference was observed in the weights of the organs of these rats as compared with those of rats receiving desoxycorticosterone in the form of pellets only. Therefore, in Table 1, the data of these two groups have been pooled.

For the same reason the data from the two experiments have been pooled in the tables in the case of control rats or rats injected with testosterone propionate alone.

In other respects the conditions of the experiments were the same as those described in our previous papers. The diet was similar to that previously described [Hall & Korenchevsky, 1938] except that fish was not always obtainable, and the yeast used, although obtained from the same source, was poorer in B-vitamins.

The weights of the organs were also calculated per unit of body weight, but for economy of space the results are not tabulated here. When of importance, they will be discussed in the text.

Effect of gonadectomy and of sex hormones

In both males and females the effects of gonadectomy (Tables 1 and 2, col. II), male sex hormones (Table 1, cols. V and VIII; Table 2, col. V) and oestrogens (Table 1, col. XIV; Table 2, cols. VIII and XI) were similar to those described in our previous papers [1933–41].

Thus, the *body weight* of castrated males was less, and of ovariectomized females was greater than that (col. I) of the respective normal controls. In both sexes the male hormones, in the comparatively small doses used, caused a slight increase in the body weight when compared with gonadectomized controls. Oestrogens, on the other hand, decreased the gain in body weight, as has been

noted several times in our own papers and in those of other workers. That there was only a slight depression of growth in the present experiments is explained by the use of the butyrate-benzoate ester of oestradiol, the effect of which is mild if sufficiently long intervals (in this case, at least 1 week) are allowed between the injections.

Fat deposition. The same explanation applies to the absence of any pronounced depression of fat deposition by oestradiol benzoate-butyrate (Table 2, col. XI), or even to a slight increase (Table 1, col. XIV; Table 2, col. VIII). Usually, as our previous experiments have shown, oestrogens depress fat deposition. In both sexes, androsterone caused a slight increase and testosterone propionate a slight decrease in the amount of fat deposited.

In our earlier papers we have shown that weak male hormones such as androsterone, or small doses of strong hormones cause no change or a slight increase in the amount of fat deposited; while medium doses and, especially, large doses of strong male hormones decrease the amount of adipose tissue in the organism. As has been emphasized previously [e.g. Korenchevsky, Dennison & Eldridge, 1937, 1, p. 469; 1937, 2, p. 478; Korenchevsky, Dennison & Hall, 1937, 1, p. 782; Korenchevsky, Hall & Ross, 1939, p. 214, Table 2, col. XIII] it often happens that after the administration of male hormones, while (as compared with the gonadectomized controls) fat deposition is decreased, the body weight remains unchanged or is even increased. In the present experiments this occurred in the case of testosterone propionate (Table 1, col. V). These observations appear to be important, since they suggest that the sex hormones may have anabolic properties. Thus, the increased gain in body weight is probably to be explained by an increase in the anabolic processes of building new tissues (e.g. in liver, kidneys, heart, among others) and not by a passive accumulation of fat in the organism. Instances indicating catabolic properties of large doses of oestrogens and male hormones have been given in our previous papers.

Sex organs. The usual return to or towards normal was observed, the degree of change depending upon the strength of the compound and the size of the dose. The specific effect of oestrogens on male sex organs has been fully discussed and the literature reviewed in our previous papers [e.g. Korenchevsky, 1941]. We wish to emphasize here only one detail of the effect of androsterone (a hormone naturally present in females) on the female sex organs, in confirmation of our previous observation [Korenchevsky, Hall & Burbank, 1939]. Lengthening the period of injection of this hormone increases the hypertrophy of the vagina and female preputial glands, but not of the uterus (Table 2, col. V).

Adrenals. The literature has been reviewed by Hall & Korenchevsky [1938] and Hall [1940]. In the present experiments, no effect of gonadectomy was noticed, but as before male hormones caused a decrease in weight and size of the glands, the mild effect being due to the comparatively small doses used. As before, the effect of oestrogen was not constant, but in those groups in which it was injected for a longer period (Table 2, col. XI) or in a larger dose for a long period (Table 1, col. XIV) the adrenals were definitely enlarged. Histological observations [Hall, 1940] suggest a possible explanation of these variations. Hyperaemia in the adrenals of animals treated with oestrogens varies in degree, in some cases being very pronounced. Our rats were killed by bleeding. The varying degree of hyperaemia, and the emptying of the hyperaemic areas by bleeding would have a considerable effect upon the weight of the organ.

The hypophysis was hypertrophied after prolonged injections of small doses (Table 2, col. XI) and large doses (Table 1, col. XIV) of oestrogens. In males

there was a slight 'castration' hypertrophy of the gland (Table 1, col. II) which was restored to normal by injections of androsterone (col. VIII). All these data are in agreement with our previous results [e.g. Korenchevsky, Hall & Ross, 1939].

Thymus. The literature has been reviewed and the results of our previous experiments summarised by Ross & Korenchevsky [1941]. The thymus, which is always enlarged after gonadectomy, decreases in size and weight after injections of male hormones and oestrogens. In the present experiments the only exception to this rule was the absence of the usual response of the thymus to injections of androsterone in females (Table 2, col. V). This sometimes happens after treatment with weak hormones or small doses of strong hormones.

Liver, kidneys and heart. Again our present data confirm our previous results, showing hepato-, nephro- and cardio-trophic properties of male hormones. Thus a slight atrophy of these organs is obtained after castration in males (Table 1, col. II) and a return towards normal after injections of male hormones (Table 1, cols. V and VIII) but not of oestrogens. Gonadectomy (as also in these experiments) does not usually have an atrophying effect on these organs in females. Still, the hepato-, nephro- and cardio-trophic properties of male hormones are clearly demonstrated also by the effects of the injections into gonadectomized females in which the liver, kidneys and heart become larger than in the intact or gonadectomized uninjected controls (compare Table 2, col. V with cols. I and II).

In rats of the same breed, kept under the same conditions and on the same diet, the liver, kidneys and heart are larger in males than in females. Therefore in our previous paper we defined the action of male hormones on the liver, kidneys and heart of females as a masculinizing effect [Korenchevsky, Hall Burbank & Cohen, 1941, p. 398].

As before, the effect of oestrogens on the actual weights of these organs was not constant, but a regular enlargement of liver, kidneys and heart is always shown in the relative weights. If, however, such mild and less toxic oestradiol esters as the benzoate-butyrate are used with sufficiently long intervals between the injections, it is sometimes possible to obtain hypertrophy of these organs even in actual weight, as happened, for instance, in one of the present experiments (Table 2, col. XI). These facts suggest that under certain conditions, and in the right doses, oestrogens might also possess non-sexual stimulating properties similar to those of male hormones.

All the data in our previous papers [1933-9] demonstrating the hepato-, nephro- and cardio-trophic properties of sex hormones have recently been summarized and examined in detail [Korenchevsky & Ross, 1940; Korenchevsky, Hall, Burbank & Cohen, 1941]. The nephrotrophic property of testosterone propionate has also been investigated and confirmed by Selye [1939; 1940], Ludden *et al.* [1941] and Kochakian [1941], the latter also confirming the hepato- and cardio-trophic effects.

Spleen. As found in our previous experiments, the effects of gonadectomy and of sex hormones on this organ are not constant, but in some of the experiments there were pronounced and definite changes. A detailed investigation of the data from all our experiments will be published elsewhere.

Effect of thyroid hormones

Cameron [1930] and Cameron & Carmichael [1920; 1921; 1922; 1924; 1926] give an account of the literature and describe their own numerous and important experiments.

The thyroid hormones administered by mouth in the form of dried thyroid powder produce hypertrophy of adrenals, liver, kidneys, heart and, less constantly, of spleen and lymphatic glands, loss of fat tissue, decrease of the growth rate or, with large doses, actual loss of body weight of animals. Four to seven weeks after thyroid feeding has been stopped [Cameron & Carmichael, 1922], the hypertrophied organs usually return to normal, while the animal's growth rate becomes accelerated above normal to such an extent that the weights of the treated rats usually exceed those of the controls.

Thyroxine, although found to possess every known activity of thyroid secretion, has not so far been proved with certainty to contain the maximum of thyroid activity. The best definition of the question is given by Harington [1933, p. 169]: 'it therefore seems unnecessary to assume the existence in the thyroid of any specifically active principle other than thyroxine, so long as we are careful to bear in mind that thyroxine is not to be regarded as itself the complete active principle, but is rather to be considered as the constituent which confers specific physiological properties upon a more complex molecule'. According to Cameron & Carmichael [1921] thyroxine administered by mouth produces hypertrophy of the same organs as in rats fed with thyroid powder. Sternheimer [1939], injecting thyroxine, confirmed the hypertrophy of the liver, and Uotila [1940] of adrenals. Uotila found no definite change in the weight of the testes, but a decrease of about 40% in the weight of the seminal vesicles.

In the present experiments the small dose of thyroid hormones had practically no effect in males and very little in females (Tables 1 and 2, col. III). This 'small dose' is to be considered comparatively large for rats, and the lack of response to this dose in our experiments can probably be explained by the richness of our diet in vitamin A. This vitamin has been shown to be antagonistic to the thyroid hormones and therefore more or less neutralizes their effects (see the Survey of Literature and their own experiments, Smith & Perman [1940]). With the large dose we obtained the usual effects, thus confirming the results recorded by previous authors: the growth rate, final body weight and fat deposition were decreased; adrenals, liver, kidneys, heart and, not constantly, spleen were hypertrophied. No effect was found on the weight and size of the sex organs and hypophysis of gonadectomized rats (Tables 1 and 2, col. IV). The large dose produced a definite atrophying effect on the thymus only in males. When the weights of the hypertrophied organs of gonadectomized rats treated with the large dose of thyroid hormones are compared with those of normal untreated rats, it is found that they often considerably exceeded normal level, especially in females.

Effect of desoxycorticosterone

According to Selye [1940] and Ludden *et al.* [1941], desoxycorticosterone causes enlargement of the kidneys and [Hooker & Collins, 1940] has some stimulating activity on male sex organs.

In the present experiments (Table 1, col. XI) slight hypertrophy of liver and kidneys was found, but no definite effect was noticed on the other organs examined, or on fat deposition or body weight.

Similar small changes have been obtained in another experiment of 21 days' duration (not included in the Tables) on 11 young normal males (final age 52 days): the weights in the control rats were—liver 12.0 g., kidneys 2.3 g., heart 0.949 g.; and in the injected rats—liver 12.91 g., kidneys 2.53 g., heart 1.080 g.

Correlation between the male sex and thyroid hormones

Males. When castrated rats were treated simultaneously with both thyroid and sex hormones, the effect obtained (Table 1, cols. VI, VII, IX, and X) did not exceed that produced by each hormone separately in the case of thymus, liver, kidneys, spleen, heart and fat deposition. Small changes in the weights of sex organs and hypophysis are not conclusive, unless confirmed on a larger number of animals, or unless histological examination shows some effects.

A definite neutralizing or antagonistic effect was found on adrenals: the hypertrophy of this gland produced by large doses of thyroid hormones (weight of adrenals 93 mg.) was lessened by the addition of testosterone propionate (74 mg.) or androsterone (70 mg.). As has been emphasized in our previous papers, this action on adrenals is a typical property of male hormones.

Another effect of male hormones antagonistic to that of thyroid hormones was shown in the gain in body weight: when thyroid hormones were administered alone, the gain was 27 g. with the small dose and 7 g. with the large dose; when testosterone propionate was injected simultaneously, the respective figures were 76 and 32 g. The neutralizing effect of androsterone was considerably less pronounced, the gain being 38 and 10 g. respectively, i.e. androsterone was unable to neutralize the effect of the large dose of thyroid hormones. It should be emphasized, however, that two rats of this group suffered from slight pneumonia, and perhaps the experiments now in progress on a larger number of animals will give more definite results. This can reasonably be expected when one considers the results on females described below.

Females. The antagonistic action of androsterone on the effect of thyroid hormones on adrenals and gain in body weight of females (Table 2, cols. VI and VII) was similar to that of testosterone propionate in males. For example, the gain in body weight of females treated with thyroid hormones alone was 24 g. (small dose) and 5 g. (large dose), while with simultaneous injections of androsterone these figures were 39 and 20 g. respectively.

As in males, there were no correlative changes in the weights of the sex organs, hypophysis and fat deposition in females.

A smaller thymus and larger spleen in rats treated with androsterone and the large dose of thyroid must be interpreted with caution, since the number of animals used was small, and the weights of all lymphatic organs sometimes vary considerably.

In females, unlike males, liver, kidneys and heart were in most cases larger than in rats receiving either hormone separately. When calculated per unit of body weight, however, these differences are less definite, so that in the case of these organs a co-operative stimulating activity can be suggested only with reservation.

Correlation between oestrogens and thyroid hormones

In contrast to the poor correlation with male hormones, thyroid hormones have a manifold interrelation with oestrogens as shown by both actual (Table 1, col. XV; Table 2, cols. IX and XII) and relative weights of several organs. The organs affected are the same in both sexes. The degree of correlation, however, differs in different organs and with different doses.

A weak co-operative activity, leading to slightly increased hypertrophy of the organs, seems to be present in some of the sex organs, the seminal vesicles and prostate of males, and the uterus and vagina of females. There is, however, no stimulating effect on the penis of males, or the preputial glands of either sex.

Because of this weak co-operative activity on the sex organs, it will be necessary to confirm the conclusions by histological investigation.

Pronounced co-operative activity of thyroid hormones and oestrogens is shown in both sexes by greater hypertrophy of adrenals, liver, kidneys and heart in rats treated with both hormones as compared with those given either hormone separately (compare in Table 1, col. XV with cols. III and XIV and in Table 2, col. XII with cols. IV and XI); or by the return to normal of the liver, kidneys and heart, the development of which is depressed by oestradiol alone (compare in Table 2, col. IX with cols. III and VIII). The fact that there is a greater loss of fat, and a decrease in the growth rate or a greater loss of body weight when both hormones are given together than when each is given separately, can also be considered as a form of co-operative activity.

The weight of the thymus remains unchanged or is even slightly increased, while the spleen, which becomes smaller after oestrogen treatment, is enlarged when both hormones are given together.

Correlation between oestrogens, thyroid hormone and androsterone in females

Since these three groups of hormones are naturally present in the female organism, simultaneous administration of these compounds to gonadectomized females was undertaken, in one experiment using a small dose (Table 2, col. X) and in another experiment a large dose (col. XIII) of thyroid hormones.

In both experiments better development of the uterus and vagina, and in one experiment (col. XIII) of the preputial glands was obtained. It is noteworthy that this co-operative activity was considerably more pronounced when the larger dose of thyroid hormones was used (col. XIII) although thyroid hormones when injected alone (cols. III and IV) have no definite effect on the weight of the sex organs.

When the small dose of thyroid hormones was combined with androsterone and oestrogens, a slightly better development of liver and kidneys was obtained which, however, did not reach those of androsterone-injected (col. V) rats. As this was not shown by the relative weights of these organs, however, the enlargement must be ascribed at least in part to the greater body weight of the animals of this group.

As shown above, decrease of growth rate or loss of body weight and loss of fat tissue, and also hypertrophy of adrenals are considerably intensified when oestrogens and thyroid hormones are administered simultaneously. Androsterone, when given in combination with these two compounds, had only a weak neutralizing (antagonistic) effect, especially when the large dose of thyroid was used. In the case of adrenals, this neutralization was insignificant. As described above, however, the neutralizing effect of androsterone was considerable when it was given in combination with thyroid hormones alone. This indicates that, as with every regulating mechanism, there are limits beyond which the regulating adjustment becomes inefficient.

Correlation between desoxycorticosterone and thyroid hormones in males

As shown in Table 1, cols. XII and XIII, no definite correlative changes were noticed in the sex organs, adrenals, hypophysis and thymus of rats injected with these two hormones.

Some neutralizing effect of desoxycorticosterone, similar to that of male hormones, on the changes produced by small doses of thyroid was present in the

case of gain in body weight and fat deposition, which showed an improvement when compared with the effects of the small dose of thyroid hormones alone (Table 1, col. III). However, this neutralizing effect did not appear when the large dose of thyroid hormones was used in combination with desoxycorticosterone (col. XIII).

A definite co-operative activity, especially with the small dose of thyroid hormones, was present in the case of liver, kidneys, spleen and heart. These organs were considerably larger when both hormones were combined than when either was given separately.

Before summarizing our results, it must be emphasized that all our statements are valid only for the correlative changes in weight of the organs. Histological and chemical investigation and new experiments approaching the problem from a different angle will make clearer and more precise the interrelation of the hormones.

SUMMARY

1. Ten intact normal and 176 gonadectomized male and female rats were used in order to investigate the possible correlation between the sex and thyroid hormones and desoxycorticosterone, as judged by changes in the weights of the organs.

2. The changes produced by gonadectomy and the injections of sex hormones described in our previous papers were confirmed, including hepato-, nephro- and cardio-trophic properties of male sex hormones and, possibly, of some oestrogenic compounds.

3. The effects of thyroid hormones found previously by other workers were also confirmed. Our large dose produced decreased gain in body weight, loss of fat tissue, hypertrophy of adrenals, liver, kidneys and heart.

4. The small dose of thyroid hormones used in our experiments, although producing only slight or no changes when administered alone, yet had definite and sometimes very pronounced effects, co-operative with or antagonistic to the other hormones in several instances.

5. Desoxycorticosterone when injected alone produced only slight hypertrophy of the kidneys (confirming the results of previous workers) and of the liver.

6. The co-operative activity of thyroid hormones with oestrogens was manifested in a slightly increased hypertrophy of some of the sex organs. In females this co-operative effect was enhanced when a third hormone naturally present in females, namely androsterone, was given simultaneously.

7. Another form of co-operative activity was shown by an increase of the hypertrophy produced by thyroid hormones in liver, kidneys and heart, when oestrogens (in both sexes), or desoxycorticosterone (in males) or possibly male hormones (in females) were administered simultaneously with the thyroid hormones.

8. Co-operative activity between oestrogens and thyroid hormones was also apparent in the increased size and weight of adrenals, slower growth rate or greater loss of body weight and greater loss of fat tissue when the two hormones were combined than when each was given alone.

9. Antagonistic (neutralizing) activity of male hormones appeared in a return towards normal level of the gain in body weight and fat deposition depressed by thyroid hormones alone or in combination with oestrogens. Testosterone propionate was more effective in this respect than androsterone.

10. Another effect of androsterone and testosterone propionate antagonistic to thyroid hormones was shown in some reduction of the hypertrophy produced

in the adrenals by thyroid hormones, but this neutralizing property of androsterone was apparently ineffective in reducing the greatest degree of adrenal hypertrophy produced by simultaneous injections of oestrogens and thyroid hormones.

Grants from the Medical Research Council and the Lister Institute have enabled us to carry out this work and to them our thanks are due. We are much indebted to Messrs Ciba Ltd., in particular to Dr K. Miescher, for the generous supply of the hormones, and also to Messrs Parke, Davis and Co. for the supply of thyroid powder.

REFERENCES

- Cameron (1930). *Canad. med. Ass. J.* **22**, 240.
— & Carmichael (1920). *J. biol. Chem.* **45**, 69.
— — (1921). *J. biol. Chem.* **46**, 35.
— — (1922). *Trans. roy. Soc. Can.* **16**, 57.
— — (1924). *Trans. roy. Soc. Can.* **8**, 105.
— — (1926). *Trans. roy. Soc. Can.* **20**, 1.
Cramer (1928). Fever, heat regulation, climate and the thyroid-adrenal apparatus.
London: Longmans, Green and Co.
Crotti (1938). Diseases of the thyroid, parathyroids and thymus. 3rd ed. London.
Grollman (1936). The adrenals. London: Ballière, Tindall and Cox.
Harington (1933). The thyroid gland, its chemistry and physiology. London.
Hall (1940). *J. Path. Bact.* **51**, 75.
— & Korenchevsky (1937–38). *J. Physiol.* **91**, 365.
— — (1938). *Brit. med. J.* **1**, 438.
Hooker & Collins (1940). *Endocrinology*, **26**, 269.
Kochakian (1941). *Endocrinology*, **28**, 478.
Korenchevsky (1941). *J. Path. Bact.* **52**, 268.
— Burbank & Hall (1939). *Biochem. J.* **33**, 366.
— & Dennison (1934). *Biochem. J.* **28**, 1474.
— — (1936). *Biochem. J.* **30**, 1514.
— & Brovsin (1936). *Biochem. J.* **30**, 558.
— & Eldridge (1937, 1). *Biochem. J.* **31**, 467.
— — (1937, 2). *Biochem. J.* **31**, 475.
— & Hall (1937, 1). *Biochem. J.* **31**, 780.
— — (1937, 2). *Biochem. J.* **31**, 1434.
— & Kohn-Speyer (1933, 1). *Biochem. J.* **27**, 557.
— — (1933, 2). *Biochem. J.* **27**, 1506.
— & Levy Simpson (1935). *Biochem. J.* **29**, 2534.
— & Hall (1939). *Brit. med. J.* **1**, 4.
— — (1940). *J. Path. Bact.* **50**, 295.
— & Burbank (1939). *Biochem. J.* **33**, 372.
— — & Cohen (1941). *Brit. med. J.* **1**, 396.
— & Ross (1939). *Biochem. J.* **33**, 36.
— & Ross (1939). *Biochem. J.* **33**, 213.
— & Ross (1940). *Brit. med. J.* **1**, 645.
Ludden, Krueger & Wright (1941). *Endocrinology*, **28**, 619.
Means (1937). The thyroid and its diseases. Philadelphia, Montreal, London.
Ross & Korenchevsky (1941). *J. Path. Bact.* **52**, 349.
Selye (1939). *J. Urol.* **42**, 637.
— (1940). *Canad. med. Ass. J.* **42**, 113.
Smith & Perman (1940). *Endocrinology*, **27**, 110.
Sternheimer (1939). *Endocrinology*, **25**, 899.
Uotila (1940). *Endocrinology*, **26**, 129.