HEPATOTROPHIC AND CARDIOTROPHIC PROPERTIES OF SEX HORMONES

BY

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In earlier papers by Korenchevsky and co-workers (1933-40) the manifold effects produced by sex hormones on the non-sex organs have been repeatedly emphasized on the basis of (1) the changes in weight of the organs of gonadectomized rats as compared with those of normal intact animals; (2) the changes in weight of the organs of rats injected with various sex hormones as compared with those of uninjected litter-mates. The microscopical changes produced in some of the non-sex organs of the rats described in these papers have been examined, and the literature on the subject reviewed in the case of adrenals of males and females (Hall and Korenchevsky, 1938b; Hall, 1940), liver of males (Hall and Korenchevsky, 1938a), and kidneys of both sexes (Korenchevsky and Ross, 1940).

In the present paper the weights of the liver and heart of 281 male and 503 female rats from all our experiments, published and unpublished, have been divided into three series according to age and duration of hormone administration, and the data from each series have been pooled and statistically analysed. The other methods of examination of the organs are given below. In the experiments on females special attention has been paid to two male hormones, androsterone and transdehydroandrosterone, since both are naturally present in the female organism (Callow, 1936; Callow and Callow, 1938); and in the experiments on males to the effects of oestrogens, since large quantities of oestrone have been found in male urine (Häussler, 1934; Deulofeu and Ferrari, 1934, 1935; Zondek, 1934; Cartland, Meyer, Miller, and Rutz, 1935; Girard, 1938), and oestrone and oestradiol have been isolated in the pure form and in large quantities from the testes (Beall, 1940).

Technique

The general technique has been described in previous papers. The male rats have been grouped as follows: Series I and II (Table I) include experiments of 20 to 24 days' (in most cases 21 days') duration on rats aged 71 to 100 days (Series I) and 101 to 150 days (Series II). Series III refers to rats 137 to 177 days old injected with sex hormones for a longer period, varying from two to four, mostly three, months. Series I to III of the experiments on female rats (Table II) correspond in length of treatment to those on males, but the ages of the animals were 60 to 85 days (Series I), 86 to 125 (Series II), and 110 to 214 days, mostly about 150 days (Series III). The following hormones were used in the doses stated (mg. per week):

	Series I and II	Series III
<i>Male Hormones</i>		
Androsterone	6.3-25.2	7.5
Androstenediol	2.45-25.2	—
Transdehydroandrosterone	7.0-28.0	7.5
Testosterone pure	1.17-10.5	0.75-7.5
Testosterone P (propionate)	1.17-10.5	0.75-7.5
Testosterone D (dipropionate)	1.05-10.5	7.5
Δ^4 -androstenedione	3.5-21.0	—
<i>Female Hormones</i>		
Oestrone	0.014-0.024	—
Oestradiol D (dipropionate) or BB (3-benzoate-17-n-butylate)	0.018-0.09	0.018-0.2

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In the tables a particular male or female hormone or a special dose is noted only when this hormone or dose had a considerably different effect on the liver or heart; the doses given in the tables are in mg. per week.

Sections were stained with haematoxylin and eosin and, when necessary, Masson's trichromic stain and scharlach red, and the usual microscopical investigation was made. In addition, in order to compare the size of the liver cells, the same technique of counting the number of cells in an area of known size with the aid of a camera lucida was used as in our previous paper (Hall and Korenchevsky, 1938a). In the present paper the cells were counted at a lower magnification than in the previous one; in this way a larger number of cells were contained in the measured area, which, it was felt, would lead to greater accuracy in the results. In Series I and II, Table I, the data for the number of cells are taken from our previous paper and multiplied by 2 in order to make them comparable to the figures of Series III.

In order to measure the heart-muscle fibres a technique was used similar to that described in our paper on kidneys (Korenchevsky and Ross, 1940). Longitudinal fibres were outlined on a measured area of paper (7.5 × 12.5 cm.), which had been previously weighed; the intermuscular spaces were then cut away, and the paper replicas of the fibres thus obtained were weighed. This weight was corrected to a standard weight of the paper, since different sheets and even different parts of the same sheet were found to vary in weight. Five areas from each heart were drawn and weighed in this way, and the average obtained represented the measurement of the muscle fibres. These measurements of liver cells were made in about a half, and of heart fibres in about one-third, of the total number of rats.

The technique used on the isolated hearts of rats will be described in detail elsewhere.

Statistical Treatment of the Results.—The data presented in the tables which follow were analysed by one of us (J. Cohen) by means of Fisher's t-test (Fisher, 1936). For the sake of simplicity the statistical significance (abbreviated "S.S.") is briefly given in the appropriate places in brackets. Thus "(S.S. 1:100)," for example, means that the observed difference between the means of two groups could occur by chance less than once in 100 such experiments. Not all the differences attain the same level of significance. The majority by far would have occurred less than once in 100 cases in random sampling. Many, however, would have occurred less than once in 1,000 or even 5,000 cases. All the instances where the statistical significance reaches or exceeds the level of 1 per 1,000 (by chance) are expressed as "S.S. 1:1,000."

Changes in Body Weight and Fat Deposition.—These changes are given in Tables I and II. They will not be discussed in detail here, but as they might have a considerable effect on the changes in weight and size of the organs they will be referred to, when necessary, in order to understand the mechanism of the weight changes in the liver and heart.

Effect of Gonadectomy

It is necessary to remember that in general, as compared with normal controls, castrated rats become lighter (S.S. 1:100) and ovariectomized rats heavier (S.S. 1:100-1,000), the changes usually becoming most clear during the later periods after gonadectomy, when there is also a tendency in most animals to increased fat deposition.

The liver in males becomes lighter both in actual weight (S.S. 1:100-1,000) and per unit of body weight (S.S. 1:20-1,000), whereas in females only the latter weight decreases (Series II and III, S.S. 1:1,000), the actual weight remaining unchanged or even slightly increasing. It is

TABLE I.—*Effect of Sex Hormones on Body Weight, Retroperitoneal Fat, Liver, and Heart of Male Rats*

No. of Series	Group of Rats				No. of Rats	Final Body Weight (gm.)	Weight of Retroperitoneal Fat (gm.)		Liver			Heart		
									Weight (gm.)		No. of Cells*	Weight (mg.)		
							Actual	Per 200 gm. of Body Weight	Actual	Per 200 gm. of Body Weight		Actual	Per 200 gm. of Body Weight	Paper Replicas of One Muscle Fibre†
I	1. Normal controls	..	..	..	26	325	12	7	12.25	7.56	114	911	563	—
II	2. " "	..	..	..	14	380	12	6	13.48	7.14		1,027	549	—
III	3. " "	..	..	..	14	436	16	7	12.98	5.95		1,136	522	28
I	4. Castrated controls	..	..	..	33	297	12	8	10.17	6.59	112	829	557	—
II	5. " "	..	..	..	25	327	13	8	9.72	5.93		865	529	—
III	6. " "	..	..	..	13	377	18	9	10.42	5.51		934	496	22
Castrated rats injected with :														
III	7. Oestradiol D	..	..	..	10	246	10	8	9.41	7.62	129	847	694	23
I	8. Male hormones	..	..	..	71	315	12	8	12.28	7.77	142	938	593	—
II	9. " "	..	..	..	14	330	12	7	11.65	7.09		991	603	—
III	10. " " (weak doses of hormones)	..	..	..	15	398	17	9	12.74	6.40		1,115	561	24
III	11. " " (large dose of testosterone P)	..	..	..	7	335	9	5	11.15	6.64	111	1,127	673	26
I	12. " " +oestrone	..	..	..	16	280	10	7	9.52	6.84	124	825	591	—
III	13. " " +small dose of oestradiol D	..	..	..	11	313	13	8	11.42	7.32	124	976	628	22
III	14. " " +large dose of oestradiol D	..	..	..	12	240	7	6	8.69	7.27	135	822	690	23

* The greater the number of cells in the measured area the smaller they are, and vice versa.

† The heavier the replicas, the larger the muscle fibres.

TABLE II.—*Effect of Sex Hormones on Body Weight, Abdominal Fat, Liver, and Heart of Female Rats*

No. of Series	Group of Rats	No. of Rats	Final Body Weight (gm.)	Weight of Abdominal Fat (gm.)		Liver			Heart		
				Actual	Per 200 gm. of Body Weight	Weight (gm.)		No. of Cells	Weight (mg.)		
						Actual	Per 200 gm. of Body Weight		Actual	Per 200 gm. of Body Weight	Paper Replicas of One Muscle Fibre
I	1. Normal controls	30	202	10	10	7.84	7.81	—	677	670	—
II	2. " "	10	232	18	15	8.25	7.15	—	726	628	—
III	3. " "	17	254	18	14	8.39	6.51	123	765	594	21
I	4. Spayed controls	45	237	12	10	8.77	7.50	—	718	619	—
II	5. " "	24	264	16	12	8.04	6.15	—	734	561	—
III	6. " "	17	328	23	14	9.23	5.63	126	799	492	21
Spayed rats injected with :											
I	7. Oestrone	31	188	8	8	7.05	7.54	—	609	650	—
II	8. " "	12	248	16	13	7.46	6.04	—	723	589	—
III	9. Oestradiol D 0.018	13	207	7	6	9.03	8.77	—	747	726	—
I	10. " " D or BB 0.018-0.09	9	228	10	9	8.73	7.66	—	755	669	—
II	11. " " D or BB 0.018-0.09	24	245	14	11	8.25	6.79	131	805	653	22
III	12. " " D 0.2	9	188	6	7	6.71	7.18	145	596	641	20
II	13. " " D or BB 0.018 + rest 10-52 days	16	274	15	11	10.69	7.82	110	844	620	20
I	14. Male hormones	44	228	10	9	9.94	8.80	—	725	635	—
II	15. " "	6	252	—	—	9.63	7.68	—	720	574	—
III	16. Androsterone 7.5	4	339	20	12	11.39	6.75	120	928	548	24
III	17. Transdehydroandrosterone 7.5	4	308	19	12	9.81	6.36	120	768	499	21
III	18. Testosterone P 2.25	7	314	18	11	10.42	6.65	119	935	597	22
III	19. " " P or D 7.5	10	278	11	8	10.75	7.77	111	970	701	23
I	20. Male hormones + oestrone	54	204	7	7	8.32	8.18	—	671	662	—
II	21. " "	19	263	16	12	8.46	6.47	—	767	589	—
III	22. Androsterone 7.5 + oestradiol D 0.018-0.09	14	269	14	10	9.83	7.32	131	913	670	22
III	23. Testosterone P or D + oestradiol D or BB 0.018-0.09	19	263	12	9	9.00	6.87	141	916	698	21
III	24. Testosterone P + oestradiol D 0.2	15	213	8	7	7.80	7.39	132	627	593	21

thus clear that in males castration has a depressing effect on the development of the liver. There are, however, no great histological changes in the liver in either sex. The size of the cells is unchanged or (Series III) only slightly decreased. In several cases there is an increase, sometimes considerable, in the vacuolation of the cells and the content of lipoid granules.

Similar changes occur in the weight of the heart, but they are much less pronounced: in males the actual weight becomes significantly smaller (S.S. 1:100), in females only the relative weight (S.S. 1:1,000, in the later periods after ovariectomy). Histologically no definite changes in the structure of the heart were found, except, on the average, a slight decrease in the size of the muscle fibres in males.

Effect of Oestrogens

This was similar in both sexes. The depressing effect of oestrogens on growth and body weight has been shown

by several workers, including ourselves, in our previous and present papers (in the present series S.S. 1:50-1,000 in experiments of short duration, 1:100 in those of long duration). In most cases there was also a depressing effect on fat deposition (S.S. 1:20-1,000).

The effect on the actual weight of the liver was not uniform or definite except with large doses injected for long periods (Table II, Group 12), in which case a considerable decrease in the actual weight of the liver (S.S. 1:1,000) was observed. It should be noted, however, that in all experiments with esters of oestradiol the relative weight was greater than that of control gonadectomized animals (S.S. 1:100-1,000), returning to or even exceeding the normal relative weight (Tables I and II). This fact suggests that oestrogens may in reality have a stimulating effect on the liver, which is produced in spite of, and is obscured by, the general depression of growth of the organism.

This stimulating effect on the liver was clearly demonstrated by the increase in both actual and relative weights of the organ (S.S. 1:100–1,000) and in size of the cells after administration of small doses of oestradiol esters with a rest interval of 10 to 52 days between the last injection and the date of killing (Table II, Group 13). This indicates that some of the toxic effects of oestrogens might be prevented by administering small doses of oestradiol esters with a mild action but prolonged activity.

This suggestion as to the stimulating effect of oestrogens appears to be contradicted by the results of the measurements of the liver cells, which in Groups 7 (Table I) and 7–12 (Table II) were slightly smaller in rats injected with oestrogens. When, however, sections of these livers were stained with scharlach red there was found to a great decrease in or disappearance of the lipid droplets in the cells; this gives a very probable explanation of the discrepancy and of the cause of it, since disappearance of fat from the cells should result in a decrease in their size. In agreement with this is the fact that the livers of oestrogen-treated animals are always dark brown in colour, while those of normal and especially of gonadectomized control animals are much lighter. This appears to be due to the disappearance of fat from the cells in the former animals.

The effects of oestrogens on the weight of the heart in rats of both sexes are similar to those on the weight of the liver: while, as compared with gonadectomized controls, no constant or significant effect on the actual weight of the organ was noted, the relative weight was in most cases increased (S.S. 1:100–1,000). Measurement of the muscle fibres showed no significant change, nor were any other histological changes noted.

However, the presence of an increased amount of heart tissue per unit of body weight in oestrogen-treated animals might suggest, as in the case of the liver, a stimulating effect of oestrogens on the heart. In any case, in ovariectomized animals the relative weight of the heart, which in the gonadectomized uninjected controls was decreased, was restored by oestrogens to or above the normal level.

Effect of Male Hormones

In general the effects of the various compounds of male hormones on gonadectomized animals are similar, varying only in degree. They are shown more clearly in the experiments of longer duration, on which the conclusions are mainly based. For this reason, and for economy of space, the effects of the different male hormones are given separately in some of the longer experiments only (Series III).

Transdehydroandrosterone produces the weakest effect, testosterone propionate the strongest; androsterone, especially in females, possesses all the beneficial stimulating properties without producing in some organs (e.g., the uterus) pathological effects which appear after injections of testosterone propionate. Compared with gonadectomized control animals, (1) there was a decrease in body weight (S.S. 1:20–100) and fat deposition (S.S. 1:100) only with large doses of strong male hormones (testosterone propionate); (2) in both sexes androsterone and testosterone propionate produced hypertrophy both in actual and in relative weights of liver and heart. The hypertrophy was especially pronounced in the experiments of longer duration (S.S. 1:100–1,000 for liver, 1:100 for heart), but in most cases was significant even after a short period of injections in males (S.S. 1:100–1,000).

In comparing weights of heart and liver of gonadectomized injected rats with those of the intact uninjected controls (Group I) an important difference between males and females appears: in males the weights of these organs

were returned only to or towards normal (Table I); in females (Table II, Series III) they exceeded the normal level after injections of androsterone (S.S. 1:20–100) and testosterone propionate (S.S. 1:100). Thus, in gonadectomized females, as has already been described in the case of the weight of adrenals (Hall, 1940), the male hormones have also a *masculinizing effect* on the weights of liver and heart, which approach those of the males.

Histologically, in experiments of long duration androsterone and testosterone propionate, unlike oestrogens, produced slight hypertrophy of the liver cells in both sexes, when compared with gonadectomized uninjected controls, and of heart-muscle fibres in males. In females there appeared also to be a slight increase in the thickness of the muscle fibres with these hormones (Table II, Groups 16 and 19), but the difference in the figures was very small (paper replicas weighing 21 mg. in ovariectomized controls, against 23 to 24 mg. in the injected animals). Our rats were killed by bleeding and therefore the inter-muscular spaces in the heart only very approximately can be considered to be occupied by blood vessels. When these spaces were compared as weighed paper replicas, the amount of vascular tissue was found in the case of males (Series III) to be as follows: castrated controls – 67 mg., and testosterone propionate – 75 mg. In females this difference did not appear. It appears, therefore, that the enlargement of the heart of males injected with male hormones can be explained by hypertrophy of muscular tissue, with probable hyperaemia and hypertrophy of vascular tissue. No other histological changes were found.

Effect of Male Hormones Injected Simultaneously with Oestrogens

When male hormones and oestrogens are injected simultaneously the effect of the latter dominates that of the former if large doses of oestrogens are used. Groups 14 in Table I and 24 in Table II provide good examples of this. Therefore all our statements made for oestrogens are valid also for the characterization of this action.

On the other hand, when the dose of oestrogens is comparatively small (up to 0.018 mg. per week in males—Table I, Group 13; and up to 0.09 mg. in females—Table II, Groups 22 and 23; compared respectively with Group 7 in Table I and Group 11 in Table II) the male hormones androsterone and esters of testosterone are able in most cases to neutralize some of the depressing effects of oestrogens on body growth (S.S. 1:100–1,000), liver (S.S. 1:20–1,000), and heart (S.S. 1:100).

It is necessary to emphasize one very important point—namely, that not only do the actual weights of the liver and heart in most cases exceed those of the control animals, but also the weights per unit of body weight. In females the relative weights of the heart exceed even those of the normal control animals (Groups 22 and 23 as compared with Group 3, S.S. 1:100–1,000). Therefore the addition of a small amount of oestrogens to the male hormones might in some cases (oestrogenic deficiency) increase the stimulating non-sexual properties of the male hormones, especially in females. From this point of view the natural occurrence of oestrogens in the organism, even of males, acquires a new significance in addition to their useful co-operative effect on the sex organs (see the literature and our own experiments on these organs in our previous papers, referred to below).

Effect of Male Hormones on the Isolated Heart of Castrated Rats (R. C. Burbank)*

Several experiments were performed on the isolated heart of normal and castrated rats, and of castrated rats

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injected with androsterone and testosterone propionate, in most cases for a prolonged period of two months. A detailed account of these experiments and of the technique employed will be published elsewhere. A preliminary statement is given here of the results obtained in 85 experiments on 46 male rats when the potential strength of the heart was measured in these three groups of rats. The measurements were made by attaching 10 and 15 gramme weights to the level pulled by the heart's contractions and tracing these contractions on a kymograph. The amplitude of the contractions was measured on the tracings and their number counted before and during the suspension of the weights, in both cases for a period of one minute. Woodworth's (1903, p. 228) quotient of the potential energy of the heart was used for expressing the results obtained, which have been statistically analysed by one of us (J. Cohen), using the same method as above.

These quotients of potential energy of the heart in the three groups of rats were as follows:

	Before Test	During Test
Control normal rats	81.3	73.5
Control castrated rats	71.9	60.0
Castrated rats injected with male hormones ..	78.2	81.7

A statistical analysis of the results obtained showed that during the "weight test" the hearts of the uninjected castrated control rats were weaker than either those of the uninjected normal controls (S.S. 1:50) or those of the castrated rats injected with male hormones (S.S. 1:100).

Thus the results on the isolated heart are in complete agreement with those obtained by weighing of the organs and their histological examination.

Summary and Conclusions

Experiments made with sex hormones on 281 male and 503 female rats are recorded, with the resulting effect on the weights and histological structure of liver and heart, and also on the isolated heart of 46 male rats.

Hepatotropic and cardiotropic properties are non-sexual effects of male hormones, especially of androsterone and testosterone propionate.

Taking into consideration also their nephrotrophic property, described in a previous paper, the male hormones in suitable doses might be considered as very important natural physiological stimulants of such vital organs as the liver, heart, and kidneys.

So far as it is permissible, from the results obtained on animals, to suggest a therapeutical application of sex hormones to human patients, it seems that androsterone and esters of testosterone should be tried clinically in suitable diseases of the liver, heart, and kidneys when a physiological stimulation of these organs is required.

We again emphasize the suggestion given in the paper on the clinical application of the sex hormones in kidney diseases that androsterone is preferable to the testosterone esters as a physiological stimulant of liver, heart, and kidneys in both sexes, since it produces only a weak effect on the male and female sex organs and is present naturally in both sexes. It is most inadvisable to stimulate the sex function in patients suffering from such grave diseases as those of the liver, heart, and kidneys.

There is also a possibility that small doses of some oestradiol esters with a prolonged and mild action (such as oestradiol benzoate-butyrate), administered with long intervals between the injections, may also be considered to produce stimulation of the liver, and perhaps of some other organs. Because of the toxicity of oestrogens in overdose, however, great caution is needed in their clinical application.

From this point of view, in cases of deficiency of oestrogens in the organism, the simultaneous administration of male hormones with oestrogens might be advantageous, since the former are able to neutralize to some extent the depressing and toxic effects of oestrogens.

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CHEMOTHERAPY AND CONSERVATISM IN ACUTE SUPPURATIVE OTITIS MEDIA

BY

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In the past have appeared many substantiated reports of striking results from sulphanilamide therapy, both in simple otitis and in suppurative otitis following paracentesis. An attempt is here made to assess its value in cases in which surgical intervention seemed to be urgent, but in which, nevertheless, it was purposely avoided.

Case I

A boy aged 9 returned to school with the remains of what had been called a common cold. There had been, however, an outbreak of "sore throat" in his family at the same time. He felt quite fit, and had a normal pulse and temperature, the only positive finding on physical examination being a sub-acute pharyngitis, the pharynx having the appearance of that seen the day following exfoliation in a moderately severe attack of scarlet fever. Eight days later he had had earache in the night, and the right drum was acutely inflamed in the upper half, while the postero-inferior quadrant was bulging with a bluish-grey sero-sanguineous sac extending into and resting on the adjacent canal. The left drum was normal. The temperature was 99° F., the pulse 90. Treatment with sulphanilamide was started. The sac quickly shrivelled up, leaving minute "puffs of cotton-wool" or "small snow-flakes" over the bulged area; the inflammation rapidly subsided, and in four days the drum was normal. On the following day the left ear started to behave in a manner similar to the right, responding to the same treatment in the same time. Deafness was only slight, and was very temporary.

Case II

The patient, a boy aged 8, following a cold two days previously, complained of bilateral earache which lasted the