XXVI. PROLONGED ADMINISTRATION OF SEX HORMONES TO CASTRATED RATS

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OUR previous experiments with castrated male rats have been of only 23 days' duration [see references and technique, Korenchevsky, 1937; Hall & Korenchevsky, 1938, 2]. For obvious reasons the investigation of much longer periods of injections is important from both the experimental and the clinical viewpoints. In these experiments we have used the hormones which are known to occur naturally in males—androsterone, *transdehydroandrosterone* and testosterone. Oestrone also belongs to this group of "natural" hormones, but in this investigation oestradiol dipropionate, a more active compound with a prolonged activity [Miescher *et al.* 1938] has been used. For the same reason the activity of testosterone propionate has also been investigated.

Technique

The hormones were administered for an average period of 105 days, the male hormones being injected 5 times a week, and oestradiol dipropionate 3 times a week, in the weekly doses indicated in Tables I and II. The total number of rats used for the experiments was 91, divided into 16 groups as shown in the Tables. The pure hormones were supplied by Messrs Ciba Ltd. and were dissolved in sesame oil, the single dose being injected in 0.2 ml. of the oil. The rats were castrated at the age of 22–25 days, i.e. before sexual maturity. The other details of our technique were the same as described in our previous papers.

Table I. *The effects of androsterone and transdehydroandrosterone injected alone or simultaneously with oestradiol dipropionate on actual weights of organs of castrated rats*

	I		II		III		IV		V		VI		VII		VIII	
									Androsterone 7.5 mg.		Dehydroandro- sterone 7.5 mg.					
	Control rats (oil)				Oestradiol diprop.				+ 0.090 mg. oestradiol diprop.		+ 0.090 mg. oestradiol diprop.					
	Normal	Castrated	Normal	Castrated	0.018 mg.	0.090 mg.	Alone	Alone	Alone	Alone	Alone	Alone	Alone	Alone	Alone	Alone
Seminal vesicles (mg.)	1309	12	131	129	403	153	39	74								
Prostate (mg.)	1341	62	142	144	981	791	132	219								
Penis (mg.)	364	98	132	140	289	210	158	163								
Preputial glands (mg.)	128	38	65	47	149	117	133	84								
Adrenals (mg.)	53	74	68	61	50	78	56	62								
Hypophysis (mg.)	10.0	12.1	49.1	75.4	9.9	56.8	12.8	45.7								
Thymus (mg.)	241	364	227	183	299	230	381	185								
Liver (g.)	13.13	10.43	9.60	9.29	14.60	12.53	12.35	8.59								
Kidneys (g.)	2.42	1.89	2.00	1.88	2.53	2.67	2.08	1.62								
Spleen (mg.)	803	646	593	528	1022	863	973	607								
Heart (mg.)	1135	950	868	833	1236	979	1066	785								
Retroperitoneal fat (g.)	16	20	10	10	24	17	17	7								
Final body weight (g.)	437	377	259	254	437	334	381	225								
Gain in body weight (g.)	275	243	128	95	249	132	254	111								
No. of rats in group	14	13	4	6	4	4	4	4								

Table II. *The effects of testosterone and testosterone propionate injected alone or simultaneously with oestradiol dipropionate on actual weights of organs of castrated rats*

	IX Testosterone 0.75 mg.		X Testosterone 0.75 mg.		XI Testosterone 7.5 mg.		XII Testosterone 7.5 mg.		XIII Testost. prop. 0.75 mg.		XIV Testost. prop. 0.75 mg.		XV Testost. prop. 7.5 mg.		XVI Testost. prop. 7.5 mg.	
	+ 0.018 mg. oestradiol diprop.		+ 0.090 mg. oestradiol diprop.		+ 0.018 mg. oestradiol diprop.		+ 0.090 mg. oestradiol diprop.		+ 0.018 mg. oestradiol diprop.		+ 0.090 mg. oestradiol diprop.		+ 0.018 mg. oestradiol diprop.		+ 0.090 mg. oestradiol diprop.	
	Alone		Alone		Alone		Alone		Alone		Alone		Alone		Alone	
Seminal vesicles (mg.)	95	254	812	1216	1231	1097	2526	2363								
Prostate (mg.)	217	405	720	960	1322	1161	2078	2087								
Penis (mg.)	216	227	368	338	346	301	414	379								
Preputial glands (mg.)	59	82	112	100	142	136	198	166								
Adrenals (mg.)	56	75	58	56	57	84	62	77								
Hypophysis (mg.)	13.7	30.1	11.9	64.5	11.7	36.1	9.6	21.0								
Thymus (mg.)	275	165	234	107	220	203	95	54								
Liver (g.)	10.62	10.94	11.07	8.69	12.95	10.56	11.15	8.80								
Kidneys (g.)	1.87	2.31	1.98	1.78	2.35	2.41	2.59	3.19								
Spleen (mg.)	870	805	805	666	952	855	803	755								
Heart (mg.)	954	939	1016	740	1152	1021	1127	940								
Retroperitoneal fat (g.)	13	11	12	9	17	11	9	5								
Final body weight (g.)	339	281	348	239	419	337	335	255								
Gain in body weight (g.)	229	175	208	97	275	185	177	82								
No. of rats in group	4	4	4	4	6	5	7	4								

For economy of space the weights per unit (200 g.) of body weight are not given, but they will be mentioned in the text whenever they alter the conclusion based on actual weights only.

Detailed histological results will be published elsewhere. In this paper are given only short preliminary statements without which the interpretation of the results would be difficult.

Oestradiol dipropionate will be abbreviated in the text to "oestradiol".

Effect on secondary sex organs

The effects of the prolonged injections on the seminal vesicles, prostate, coagulating glands, penis and preputial glands, atrophied after castration, were in some cases similar to, in others different from, those obtained in our previous experiments of shorter duration.

Male hormones. On the basis of the results of the present experiments the male hormones could be grouped in the following descending order of activity—testosterone propionate, testosterone, androsterone and dehydroandrosterone; only one hormone, testosterone propionate, was able to restore to normal (col. XIII), or, in large doses to produce supernormal (col. XV), development of seminal vesicles and prostate; the activity of androsterone was much more pronounced on the prostate than on the seminal vesicles (col. V). All these results were similar to those obtained in our 23-day experiments.

The prolongation of the injections strengthened the effect of androsterone, testosterone and testosterone propionate, but not that of dehydroandrosterone, which remained very weak, as comparison of the figures of Tables I and II with the data given in our previous papers [Korenchevsky *et al.* 1935-37] shows.

A close correlation was present between the degree of restoration towards normal of the weight and size of the organs and their histological structure. No pathological changes were observed, except for some abnormal vacuolation of the epithelial cells in the central and lateral lobes of the prostate in the rats injected with large doses of testosterone propionate.

Oestradiol dipropionate (cols. III and IV) increased the weight and size of the seminal vesicles to a degree remarkable for a female hormone, having a stronger effect on these organs than dehydroandrosterone. Even a definite hypertrophy of the penis was obtained, which has not previously been found with pure oestradiol or oestrone. The effect on the preputial glands, the weights of which vary considerably both in control and injected animals, was less definite. Increasing the dose from 0.018 mg. (col. III) to 0.090 mg. (col. IV) did not increase the effect on the male sex organs.

However, this remarkable effect of oestradiol on the weight and size of the seminal vesicles and prostate was not accompanied by restoration of the secretory epithelium, but was chiefly due to pathological development of fibrous tissue in these organs, while after shorter periods of injections [Korenchevsky & Dennison, 1935] the muscular layer was also greatly hypertrophied. The penis of the "oestradiol" rats showed better development of the corpora cavernosa and also partial separation of the epithelial layers of the preputium and of the glans penis, which are fused in castrated control rats. The epithelial layers showed slight development, but still resembled those in castrated control rats and not those in normal animals.

Co-operative or antagonistic activities of male and female hormones and the neutralizing effect of the male hormones on the pathological changes caused by the oestrogens

As judged by the weights of the organs, testosterone and oestradiol showed strong co-operative activity (cols. X and XII). This is in agreement with the results of our previous experiments of 23 days' duration [Korenchevsky *et al.* 1936]. This co-operative activity was confirmed histologically, especially with the large dose (col. XII); with the small dose of testosterone (col. X) the pathological effects of the oestradiol were not completely neutralized and were evident in the excessive development of fibrous tissue and stratification of the epithelium, which was, however, of the more normal columnar type. Testosterone propionate showed no co-operative activity with oestradiol (cols. XIV and XVI) in respect either of weight or histological structure; with both doses of testosterone propionate, the pathological effect of the oestradiol was seen only occasionally and in a slight degree.

The apparent absence of a co-operative activity of testosterone propionate with oestradiol is not due exclusively to the fact that the male hormone alone, in the doses used, produces normal or even supernormal development of the sex organs, so that its activity with the oestrogen is veiled. This conclusion is supported by the fact that in our previous experiments with small doses of testosterone propionate [Korenchevsky & Dennison, 1937] a similar result was obtained (only very slight effect on seminal vesicles). Slightly smaller sex organs in the rats injected with both hormones (cols. XIV and XVI) as compared with those injected with the male hormone alone (cols. XIII and XV) may be explained by the smaller size of the former rats; no such difference was seen in the weights of the organs calculated per unit of body weight.

An antagonistic effect was unexpectedly obtained when androsterone was injected simultaneously with oestradiol dipropionate (col. VI). This effect was very pronounced on the seminal vesicles (both in actual weights and those per unit of body weight), but less so on other sex organs (noticeable only in weights per unit of body weight). This antagonistic effect is the more remarkable since with smaller doses injected for shorter periods [Korenchevsky *et al.* 1935] a

definite co-operative effect of androsterone with oestrone was obtained both by weight and (unpublished data) histologically.

When *trans*dehydroandrosterone was injected simultaneously with oestradiol the weight of the seminal vesicles (74 mg. col. VIII) was less than that in rats injected with oestradiol alone (129 mg. col. IV). In this case, therefore, the male hormone exercised a definite antagonistic effect on the activity of the oestradiol. This interaction was not present in the case of the prostate and penis. Histological investigation confirmed this antagonistic activity of oestradiol with androsterone or dehydroandrosterone, at the same time revealing some neutralizing effect of these male hormones on the pathological changes produced by the oestrogen. Thus, although fibrous tissue was excessively developed and the epithelium was stratified (antagonistic "oestrogens" effect), the fibrosis was much less pronounced than with oestradiol alone, and the epithelium was of the more normal columnar type (neutralizing "male" effect).

Comparison with the effects of the same hormones on normal, non-castrated rats

In our experiments of long duration with non-castrated rats [Korenchevsky & Hall, 1939] it was unexpectedly found that the development of the secondary sex organs of these normal animals was depressed by androsterone, not significantly changed by testosterone and considerably stimulated by testosterone propionate. These remarkable differences in the activities of the male hormones were explained by the balance of two simultaneously exercised, opposite activities: (a) the depressing effect of the injected male hormones on the anterior lobe of the hypophysis, resulting in a more or less decreased secretion of gonadotropic hormones, which in turn decreases the secretion of the natural male hormones from the testes. This should produce atrophy of the secondary sex organs, but (b) this effect is counterbalanced by the stimulating effect produced directly, but in different degrees, by the injected male hormones on the secondary organs. In the case of the weaker sex hormones (androsterone and *trans*dehydroandrosterone) the atrophying effect (a) prevailed; but with testosterone propionate the hypertrophying effect (b) was the stronger. With testosterone, a hormone of medium strength, the two activities neutralized one another and therefore no change was obtained in the condition of the sex organs.

This mechanism cannot operate in the case of gonadectomized animals, and the results of our present experiments on castrated animals corroborate this; all the male hormones, without exception, produced stimulation of the secondary sex organs, the degree of stimulation produced corresponding to the strength of their sexual activity. The varying results obtained when the different male hormones were injected simultaneously with oestradiol probably depended upon the strength of the particular male hormone as compared with oestradiol. Therefore the different male hormones, when injected simultaneously with oestradiol into castrated animals, were divided according to their different degrees of activity into 3 groups, each consisting of the same hormones as in the case of normal (non-castrated) rats injected with the male hormones alone.

Effects on non-sexual organs, fat deposition and body weight

Effect of castration. We have described in our previous papers [Korenchevsky and co-workers, see references 1934–37] how castration produces more or less pronounced changes in the various non-sexual organs of the rat. The results obtained have been confirmed by our present experiments and may be summarized as follows (compare cols. I and II, Table I): varying degrees of hypertrophy of adrenals and hypophysis; delayed involution (i.e. increased size) of

the thymus; decrease in the weight of the liver, kidneys, heart and spleen (a definite change of the spleen recorded only in the present long-duration experiments); decreased growth and gain in body weight, but increased fat deposition; no definite changes in the thyroids. When calculated per unit of body weight, these changes are even more striking in the adrenals, hypophysis and thymus, but less pronounced in the other organs. Therefore a certain amount of the decrease in weight of liver, kidneys, spleen and heart corresponds to and can be explained by the smaller size and weight of the castrated animal. Part of this "oligosplanchnia" should, however, be explained by the specific effect of gonadectomy, i.e. by the absence of secretion of the testicular hormones. Specific histological changes after castration are well known and have been found in the hypophysis by several workers and in the adrenals by Deanesly [1928], Andersen & Kennedy [1933], Deanesly & Parkes [1937], Cramer & Horning [1937], Hall & Korenchevsky [1937; 1938, 1]. In the liver only a slight decrease in the size of the lobules has been observed [Hall & Korenchevsky, 1938, 2]. Histological examination of the other organs investigated in the present experiments has not yet been completed.

Effects of the hormones

Gain in body weight. The figures given in the Tables for the gain in body-weight during the experiment, taken in conjunction with the figures for the final body weight, strongly indicate an effect of the sex hormones upon metabolism. While oestradiol (cols. III and IV) produces a pronounced decrease in body weight resulting in stunted growth, with the male hormones this depressing effect is absent (androsterone, *trans*dehydroandrosterone, small doses of testosterone and testosterone propionate, cols. V, VII, IX, XIII) or less pronounced (large doses of testosterone and testosterone propionate cols. XI and XV). Moreover, this depressing effect of oestradiol can be partly neutralized by the simultaneous injection of male hormones (cols. VI, VIII, X, XIV) except in the cases of large doses of testosterone and testosterone propionate (cols. XII and XVI). These exceptions are interesting and important in that they demonstrate qualitatively different effects of different doses, which property is well known in pharmacology for several compounds and in endocrinology is especially important in the case of simultaneous injections of oestrogens and progesterone.

That the effect on the body weight is dependent upon the size of the dose is in most cases confirmed by comparison of the data of our present experiments with the results previously obtained. When injected for shorter periods (i.e. total dose being smaller), androsterone [Korenchevsky *et al.* 1935], testosterone [Korenchevsky *et al.* 1936] and small doses of testosterone propionate [Korenchevsky *et al.* 1937] caused increased gain in body weight, while large doses of testosterone propionate gave the same decrease, and dehydroandrosterone the same absence of effect both in long and short duration experiments.

A definite neutralizing property on the depressing effect of oestradiol is noteworthy in the weak sex hormones, androsterone and even to some extent dehydroandrosterone.

Fat deposition. With the exception of androsterone all the hormones investigated (including oestradiol) decreased, in varying degree, the amount of fat deposited. The depressing effect of oestradiol on the deposition of fat was considerably neutralized by simultaneous injections of androsterone, but not affected by small doses of testosterone and testosterone propionate, while dehydroandrosterone and large doses of testosterone and testosterone propionate when injected simultaneously with oestradiol caused an even greater loss of fat.

With shorter periods of injections (see references mentioned above), androsterone, dehydroandrosterone and testosterone produced no change in the fat deposition, while testosterone propionate decreased it as in the present prolonged experiments.

Adrenals. The hypertrophied "castration" adrenals (col. II), as judged by weight, both actual and per unit of body weight, returned to or towards normal (cols. V, VII, IX, XI, XIII and XV) after prolonged injections of male hormones, the changes both in weight and histologically being similar to those previously obtained in experiments of 3 weeks' duration [Hall & Korenchevsky, 1937; 1938, 1]. Large doses of testosterone propionate caused abnormal depletion of lipoid from some parts of the cortex. It is remarkable, however, that the longer period of injections did not, as one would theoretically expect, cause greater, but rather less pronounced, changes, as though some kind of neutralizing mechanism had developed during the prolonged administration of the male hormones.

When oestradiol was injected alone, the actual weight of the "castration" adrenal was slightly decreased but, when the weights are calculated per unit of body weight, a definite increase is observed with both doses (an average of 53 and 48 mg. in the injected rats as compared with 38 mg. in the control castrated animals). Evidently the weight of the adrenals was only slightly decreased in correlation with the stunted growth of the "oestradiol" rats, but the effect of the oestradiol on the adrenals is essentially hypertrophying. This conclusion is corroborated in a different way in most of the groups in which male and female hormones have been injected simultaneously (cols. VI, VIII, X, XIV, XVI): in these cases an abnormal hypertrophy of the adrenals occurred even in actual weights. A similar interrelation has been recorded in experiments of 3 weeks' duration [Korenchevsky and co-workers, 1935-37]. Previously also in experiments of shorter duration, Korenchevsky & Dennison [1934] found that oestrone produced hypertrophy in normal, but not in castrated, rats.

Histologically, oestradiol produced hyperaemia, a narrower *zona glomerulosa* with some atrophy of its cells, patches of peculiar amyloid-like degeneration in the *zona reticularis*, and the appearance of "nests" of specific cells at the boundary between the cortex and the medulla.

These "oestradiol" changes in the adrenals were not completely neutralized by the simultaneous injection of male hormones, thus corroborating the results obtained by weights.

Hypophysis. It is now well established that oestrogens produce enlargement of the anterior lobe of the hypophysis, resulting, with sufficiently large doses, in a tumour-like hyperplasia of the gland. In our present experiments we also have obtained similar changes in weight (Table I, cols. III and IV) and size of the hypophysis.

Male hormones alone, in both our previous and present experiments and in those of other workers, had no considerable or constant effect on the size and weight of the hypophysis. Allanson [1937] has given a good review of the literature on the subject and added her own histological results.

In our previous experiments of 3 weeks' duration, the weight of the "castration" hypophysis was decreased to normal only after injections of androsterone. In the present long-duration experiments this recovery was effected by androsterone (col. V) and also by large doses of testosterone propionate (col. XV).

It is necessary to emphasize the most important result that all the male hormones used were able to prevent to some extent development of the hypophysial hypertrophy caused by oestradiol, the greatest effect being produced

by the large dose of testosterone propionate (col. XVI, average weight 21 mg. as compared with 75.4 mg. in the rats injected with oestradiol alone). In one of the rats of this group (testosterone propionate + oestradiol) the hypophysis weighed 14 mg., which weight is within the variations present in the control uninjected groups.

Wolfe & Hamilton [1937], in experiments of 10 days' duration, also noticed some suppression of oestrogenic changes in the hypophysis by male hormones. Thus a definite antagonistic interrelation between male and female hormones is apparent in their effects on the hypophysis.

Thymus. All the hormones, except dehydroandrosterone, hastened the involution of the thymus, and the simultaneous injection of oestradiol and male hormones had a co-operative effect, these results being similar to those obtained in our shorter-duration experiments (see references already mentioned).

Liver, kidneys, spleen and heart. From a study of the data given in Tables I and II, it is possible to come to a general conclusion that male hormones cause an increase, and oestradiol (except in kidneys) a decrease, in the weights of these organs in most rats. Dehydroandrosterone and large doses of testosterone and testosterone propionate appear to increase this "oligosplanchnic" effect of oestradiol. Androsterone, on the contrary, is able to neutralize this effect, even when large doses of oestradiol are given, while in the cases of testosterone and testosterone propionate this neutralization occurs only with small doses of oestradiol. However, for true megalo- or oligo-splanchnia, not only the actual weights, but also the weights per unit of body weight should show the same change, i.e. the changes in weight of the organs should be at least partly independent of the changes in weight and size of the animals. If the changes we have obtained are considered from this point of view, and the weights per unit of body weight (not included in the Tables) are also taken into consideration, the following conclusions are reached:

(1) The male hormones can be considered as true stimulators of certain organs in castrated rats, but not in normal animals [cf. Korenchevsky & Hall, 1939]. In other words, they restore the size and weight of the liver, kidneys, spleen and heart to or towards normal, but are unable to cause supernormal enlargement.

(2) It is remarkable that this stimulating activity should be most strongly manifested, not by the most sexually active hormone, testosterone propionate, but by the relatively weak sex hormone, androsterone.

(3) The female hormone, oestradiol dipropionate, can be regarded as a stimulator only when the weights are calculated per unit of body weight (e.g. these weights of liver, kidneys and heart in rats injected with oestradiol were respectively 7.4, 1.5 and 0.66 g. as compared with 5.5, 1.0 and 0.49 g. in castrated control rats).

(4) Since the body fat in the "oestradiol" rats is much decreased, a comparison with the much fatter control animals is difficult. From the point of view of metabolism, one unit of passive fat tissue requires much less activity of the organs regulating metabolism (liver, kidneys, endocrines etc.) than do the more active tissues (e.g. muscular, glandular, nervous etc.). Therefore in fat animals one would expect that the weights of these "metabolism" organs, when calculated per unit of body weight, should be smaller than in animals in which the amount of body fat is small, provided that the metabolic rate is about the same.

According to Reed *et al.* [1930] the amount of genital and retroperitoneal fat in rats represents about 32% of the whole adipose tissue in the body. According to our observations, the amounts of these two types of fat (as

dissected by us) are about equal (i.e. 16%). If in all groups of our rats the total body fat is calculated on this basis and subtracted from the final body weight, the remaining weight will represent, at least chiefly, the approximate weight of the active tissues in the body. Even with this correction the weights per unit of body weight of the liver, kidneys and heart are heavier in the oestradiol rats than in the castrated control animals (9.8, 2.0 and 0.88 g. respectively, as compared with 8.5, 1.5 and 0.75 g.). It must, however, be admitted that this correction is neither perfect nor complete, since the amount of fat present in the cells of the organs is not taken into consideration.

Macroscopically it was noticed that the livers of castrated control rats were light brown in colour, sharply differing from the dark, reddish-brown livers of the "oestradiol" rats. Preliminary histological investigation has shown that this difference in colour is due partly to hyperaemia in the livers of the oestradiol rats and partly to the much reduced amount of fat and lipoids in the liver cells of these animals as compared with those of castrated controls. These changes were present also in the livers of rats injected simultaneously with oestradiol and male hormones. No pathological changes were found in the livers after injections of male hormones alone, such livers appearing normal.

The changes in weight of the organs and the results of preliminary histological investigation of the liver and kidneys suggest that the male sex hormones most probably have a favourable stimulating effect upon the liver, kidneys, heart and spleen of castrated rats. At present the true nature of the activity of oestradiol on these organs is difficult to define until histological investigation is completed. The changes per unit of body weight, however, especially in the case of kidneys, may possibly indicate that oestrogens also have some stimulating effect upon these organs, veiled, however, by the stunted growth of the organism and fat impoverishment of the body.

Comparison of the effects on non-sexual organs with those on sexual organs

Two important points must be emphasized in the nature of the reaction of the different organs to castration and injections of the sex hormones:

(1) Castration and the injection of sex hormones into gonadectomized rats always cause typical changes in the sexual organs of every animal, while, in most cases, the weights of the non-sexual organs, fat deposition and gain in body weight are changed only in the majority of animals, the average figures, however, showing typical changes. If, however, the effects produced by the hormones are studied within the same litter, the rats of which are divided into the different groups, the number of animals showing the same typical changes is much increased, in several cases the exceptions being absent. The importance of comparison with control animals of the same litter has been emphasized in our previous papers [Korenchevsky, 1932; Korenchevsky *et al.* 1932; Korenchevsky & Dennison, 1934]. However, in the present experiments comprising 16 groups this was impossible, as our litters consisted of 4-8 rats only, which were divided into as many groups as possible.

(2) While prolongation of the injections of all hormones, except dehydroandrosterone, caused an increase in the effect upon the sexual organs, the effect upon the non-sexual organs was not increased, but even in some cases (e.g. testosterone) decreased. Probably this difference in reaction is at least partly to be explained by the changes produced in the gain in body weight and, perhaps, fat deposition, by the prolongation of the injections. As described above, the changes in the liver, kidneys, heart and spleen are much more dependent on the body weight than are those in the sexual organs.

SUMMARY

1. The effects upon the sexual and some other organs of prolonged administration (about $3\frac{1}{2}$ months) of sex hormones to castrated rats are described and compared with the results obtained in our previous experiments of shorter duration (about 23 days). The hormones injected were oestradiol dipropionate, androsterone, *transdehydroandrosterone*, testosterone and testosterone propionate injected alone, or oestradiol dipropionate combined with the male hormones.

Effects on sexual organs

2. Prolongation of the injections was followed by a greater effect on the sexual organs in the case of androsterone, testosterone and testosterone propionate, but not of *transdehydroandrosterone*.

3. Testosterone propionate was the only hormone which produced complete restoration of the atrophied sexual organs, or, with large doses, a great super-normal development of the seminal vesicles and prostate.

4. A comparatively small dose of oestradiol dipropionate (0.018 mg. per week) produced (for a female hormone) a great enlargement of the seminal vesicles, coagulating gland, prostate and even penis, but increasing the dose did not increase the effect.

5. As with other oestrogens, this apparent return towards normal weight and size of the sexual organs was of pathological nature and caused chiefly by increased development of fibrous tissue. This fibrosis should, however, be considered as one of the specific sex effects, as it was present only in the sexual organs.

6. With the doses used oestradiol dipropionate showed pronounced co-operation in restorative activity with testosterone, but not with testosterone propionate, while an antagonistic interaction with androsterone and *transdehydroandrosterone* (in contrast to the co-operative effect of androsterone with the weaker compound, oestrone) was found.

7. The neutralizing effect of the male hormones on the pathological changes in the sexual organs, produced by as strong an oestrogen as oestradiol dipropionate, was very pronounced in the case of testosterone and testosterone propionate, but weak with androsterone and *transdehydroandrosterone*.

Body weight and fat deposition

8. Only oestradiol and, to a lesser degree, large doses of testosterone and testosterone propionate caused a decrease in the gain in body weight. Androsterone, *transdehydroandrosterone* and small doses of testosterone and testosterone propionate, although having no effect when injected alone, partly neutralized the depressing effect upon growth of the simultaneously injected oestrogens.

9. All the hormones in the doses used caused in varying degree a decrease of the amount of body fat, except androsterone, which was even able in this respect to neutralize the effect of oestradiol.

Non-sexual organs

10. All the hormones accelerated the physiological involution of the thymus and there was a co-operative relation in this respect between the male hormones and oestradiol dipropionate.

11. The male hormones prevented to a considerable degree (with testosterone propionate in some cases almost completely) the tumour-like hyperplasia of the hypophysis produced by oestrogens.

12. The male hormones in most cases caused the "castration" adrenal to return to or towards normal, while oestradiol dipropionate produced specific pathological changes in this gland which were only partly neutralized by simultaneous injections of the male hormones.

13. Slight hypertrophy of liver, kidneys, heart and spleen was produced by the male hormones in most rats but oestradiol dipropionate caused either a decrease in their actual weights or (kidneys) no change, "dark" liver being a constant feature of all rats injected with this hormone.

14. This "oligosplanchnic" effect of oestrogens was to some extent neutralized by the male hormones, the comparatively weak sex hormone, androsterone, having the greatest effect in this respect.

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