Medicine. — *Paradoxical Effect of Oestrone in Male Animals. V. Further Arguments in Favour of the Hormonal Etiology of the Hypertrophy of the Prostatic Gland.* (From the department of Pharmacology, University of Leiden.) By J. H. GAARENSTROOM, S. E. DE JONGH and D. J. KOK. (Communicated by Prof. J. V. D. HOEVE.)

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Since a couple of years a definite tendency exists to see a causative relation between the prostatic hypertrophy and a dysfunction of the testicles, the latter resulting in a change of the hormonal equilibrium (male hormone-oestrone or a comparable compound) in favour of the latter.

We will not repeat here all our arguments, but under the reference to earlier papers (1) only remind of the so-called "paradoxical" enlargement, in the castrated male animal, of the derivatives of the Wolffian duct, obtainable with oestrone injections, an enlargement, which has typical places of predilection in each species, e.g. the prostatic gland in the dog.

These not repeated arguments are based upon a great number of analogies between the enlarged prostata of the castrate, treated with oestrone and of the patient, suffering from spontaneous "prostatic hypertrophy". The imposing similitude, however, is seriously disturbed in one respect, the histological structure. The aim of this communication is to denervate the objections against our theory, based upon this difference.

In short the latter, striking as it is, can be described, e.g. for the dog, as follows:

Whereas the increase in size mainly depends upon growth of muscle and connective tissue in both cases, important difference exists in the behaviour of the epithelium. The pathological findings in the clinical picture of the hypertrophy of the prostate gland should be interpreted, after REISCHAUER (2) and POLLAK (3) as a penetration of the new-built lobes of muscular and connective tissue by the glandular tubes. The tubes are *wide*, with a well developed *cylindrical epithelium* in one layer, which has a typically male apparition. It is classified as "male", because the same strongly arborised gland-complexes, covered with a high epithelium (though surrounded with less muscle and connective tissue) can be obtained in a castrate by injection of testosterone. However, in the "artificially enlarged" prostate, solitary small glandular tubes lay here and there in the fibro-muscular tissue; they *hardly* have *any lumen*, (in young castrated animals it is rather the picture of epithelial cords), and a *low cubic epithelium*, which, if high doses of oestrone are used, even converts into the *stratified form with cornification.*

On critical study these differences yield two questions to be solved: A: What is the cause of the "male" apparition of the epithelium in the prostate of the patients, and B: why does a metaplasia into a stratified epithelium in our experimental animals exist?

The second point gave us the lesser trouble, so herewith will be done first. From earlier experiments we knew already that this is to be contributed to overdosage with oestrone. Trying to obtain a growth within some weeks for which nature takes a much longer time, we are bound to too high dosages, so that in the excretory tubes or even the glandular tubes themselves a stratified epithelium is produced. We could (1) show already that this is not a necessary detail in the syndrome of the "artificial" prostatic hypertrophy: we could double the prostata weight with low dosages of oestrone in some weeks without the least metaplasia. We are customed to use dosages, of middling height, with which an augmentation of the prostata to a manyfold of the initial weight can be obtained and with which only the biggest excretory tubes show metaplasia of the epithelium. This may remain an aesthetic shortcoming, for technical reasons the production of a considerable enlargement in not too long a period is favourable for the experiments whereas, after the above deliberations, it can be done without objections against the theory.

The first point yields more difficulties and these don't lay in the "insufficiently male" aspect of the artificial prostatic hypertrophy, but rather in the male (often excessively male) one of the spontaneous form, since we wish to relate the latter with a *shortage* of male hormone!

When indeed during the period of development of the spontaneous hypertrophy the oestronelike element relatively prevails, it must be postulated that during this time the "male" effect of testosterone on the epithelium is more easily obtained than its counteraction of the prostata growth, promoted by oestrone.

One might suppose that a higher level of testosterone in the body would cause a still more "male looking" prostatic gland, what, however, conflicts with the histological picture of this gland during the period of optimal function of the testicles. Thus, one is guided to the supposition that *the epithelial effect of testosterone is enhanced by the relatively higher level of oestrone in the animal.* For androsterone this is known since long already ("pacemaker effect" FREUD (4)). With testosterone KUN & PECZENIK (5) and VAN DER WOERD (6) saw signs of it in the rat.

When this supposition is correct, no improbability or contradiction remains: Testosterone, because of insufficient quantities, is not able to prevent the growth, caused by oestrone, but (even grace to that oestrone) it can make the epithelium keep its normal aspect. Our experiments, in order to test the above considerations, were performed with four litters of young dogs, including a total of 13 male animals.

They were castrated at an age of ca 6 weeks. A short time afterwards they underwent several treatments, that will be described later on. After

the autopsy a series of organs, under which the prostata bears the main importance, were weighed. The prostata was sectioned for histological investigation.

The treatment, body- and organweight of each dog are entabulated. The relative prostata weights refer to the body weight of the corresponding animal at autopsy, the relative dosages to the average of the body weights of the whole litter at the beginning of the experiment and at autopsy.

Litter I (Dog H.I.J.). All dogs received oestrone. Two of them moreover different quantities of testosterone.

The dosage of oestrone proved to be too low: the prostata is enlarged (cf. relative weights dogs M, P, Q and S) but not much. The quantities of testosterone, high as they were, could easily bring about a male (resp. supermale) structure in the prostatic gland. Since this was accompanied by distinct (normal!) growth, the experiment does not deliver arguments for or against our supposition.

Litter II (Dog K.L.M.).

Dosage of oestrone is doubled, testosterone far-going reduced. Third animal: control, treated with oil. Though the oestrone effect is definitely more distinct here than in dog H (as appears from weight and histological picture of the prostata (K)) testosterone easily prevails over the oestrone activity (L).

Again, however, a demonstrable, though small enlargement exists. We approach the optimal ratio between the two components, which is reached in

Litter III (Dog N.O.P., viz. fig. 1—3).

Dog O received in absolute sense somewhat less oestrone, relatively, however, somewhat more than in the foregoing experiment. In dog N this was combined with very little testosterone. Dog P received testosterone only.

In this dog P no demonstrable effect upon the prostata could be shown: no gain of weight (c.f. dog M and Q), and histologically no masculinization. In dog N the weight of the prostata is definitely lower than in dog O (absolutely as well as relatively). Nevertheless the gland had a more "male" apparition than those of dogs O and P: *instead of the epithelial cords in dogs O and P real tubes proved to have developed.*

Thus, in the presence of oestrone, the prostata-enlarging effect of which was hindered in the mean time, this quantity of testosterone revealed a masculinizing influence, to which it was not capable when acting alone.

Litter IV (dog Q, R, S, T, viz. fig. 4—7). A fourth pup in the litter produced us the advantage of an untreated control animal. For the rest it was corroborative for exp. III with a still smaller dosage of oestrone. Nevertheless the prostatic weight of the animal (T), treated with oestrone and testosterone comes again absolutely and relatively below that of the animal exclusively treated with oestrone (R); this quantity of testosterone, which alone caused no growth nor development of the prostata worth

mentioning (S) induced an epithelial development of the gland to a certain degree in dog T, that received besides testosterone oestrone.

Dog	Daily dose in γ of		Same pro av. Kg dog		Bodyweight dog in Kg			Weight Prostata in gr	Same pro Kg dog at autopsy
	Test. pr.	Oestr.	Test. pr.	Oestr.	Beginning of the experim.	End of the experim.			
H	—	30	—	12.6	1.6	3.3		0.80	0.24
I	500	30	208	12.6	1.6	3.2	2.4	1.22	0.38
J	2000	30	832	12.6	1.2	3.3		4.29	1.30
K	—	200	—	22.4	6.7	13.4		4.93	0.37
L	700	200	79	22.4	5.7	11.6	8.9	5.40	0.47
M*	—	—	—	—	5.3	10.8		1.05	0.09
N	160	133	35	29	4.0	5.3		2.43	0.46
O	—	133	—	29	3.7	5.2	4.6	3.92	0.75
P	160	—	35	—	4.5	5.1		0.53	0.10
Q*	—	—	—	—	2.7	6.0		0.45	0.08
R	—	80	—	18	2.6	5.5	4.4	1.82	0.33
S	160	—	36	—	3.1	6.5		0.60	0.09
T	160	80	36	18	2.8	6.0		1.59	0.27

* Injected with oil as a control solution.

The differences between the "artificial prostatic hypertrophy" of the castrate and the spontaneous form of the non-castrate are no doubt not entirely taken away with the above experiments, but still we are very content already, to have been able to show, that with testosterone, in certain, carefully chosen dosages, a decrease in size of the prostatic gland, without preventing the hypertrophy as a whole, can be obtained together with a glandular development in "male" sense.

It is probable, that a somewhat higher dosage of testosterone, administered over a longer period (e.g. half a year) together with oestrone, should give rise in the hypertrophied prostata to an almost complete development of the glandular tissue. This sort of experiments, in which the average relative dosage partially remains an uncertainty unto the finish because of the growth of the dog, sothat the success is technically beyond the control of the experimentator, is not very inviting and in our opinion superfluous at the progress of our experiences.

We see the etiology of the hypertrophy of the prostate as follows:

The level of testosterone-like substances in the body decreases gradually,

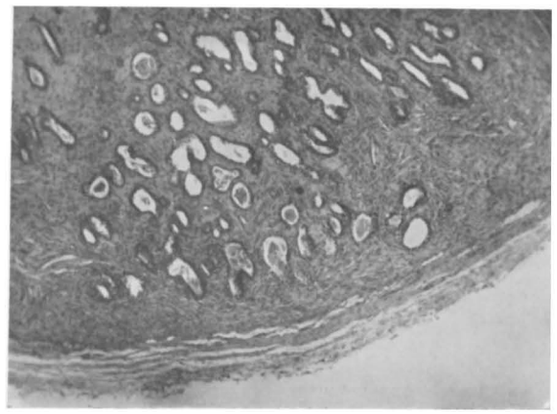

Fig. 1. N. Oestrone + testosterone prop.

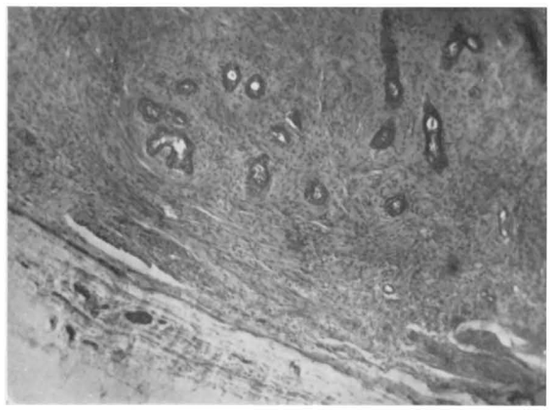

Fig. 2. O. Oestrone.

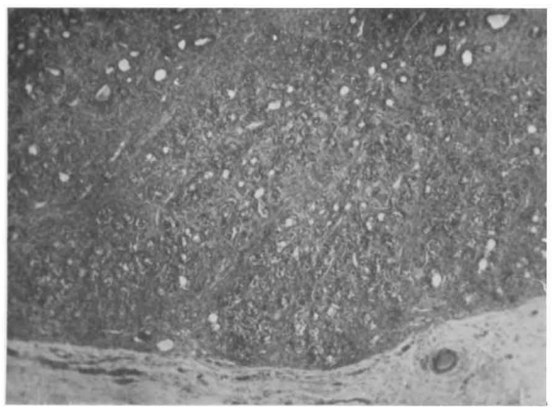

Fig. 3. P. Testosterone prop.

Fig. 1—3. Glandular part of prostatae of dogs N—P.

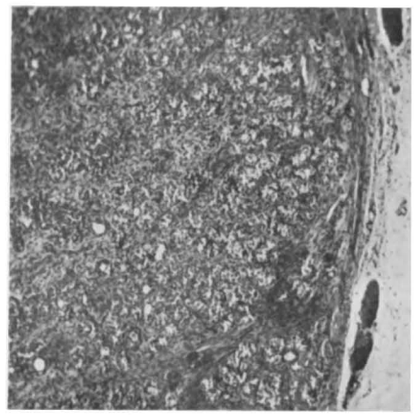

Fig. 4. Q. Oil.

Fig. 5. R. Oestrone.

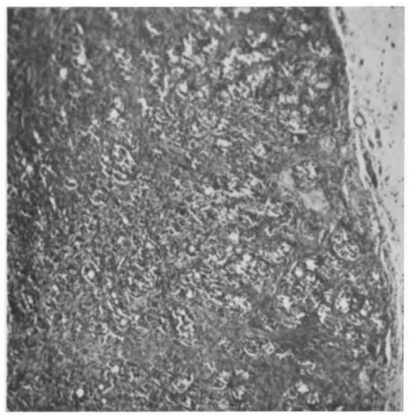

Fig. 6. S. Testosterone prop.

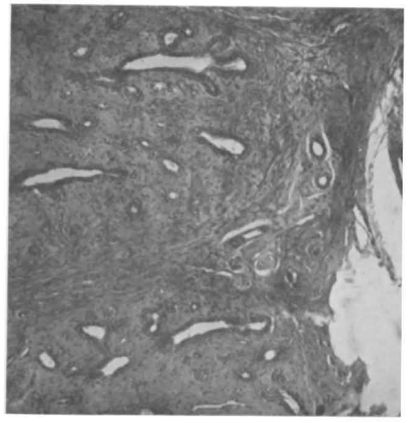

Fig. 7. T. Oestrone + testosterone prop.

Fig. 4—7. Glandular parts of dogs Q—T.

sothat the oestrone-like component increases, relatively at least. When the former level comes so low, that the oestrone effect can not be fully hindered, the prostatic hypertrophy begins by growth of muscle and connective tissue. The small quantity of testosterone is on the other hand capable, with the aid of oestrone, to make the glandular system grow, also into the new developed parts of the organ, and to procure (remain procuring) a "male" aspect to the whole gland. When in exceptional cases the testosterone level would sink still lower, the male aspect could not be maintained and the gland would obtain the appearance of the uncomplicated "oestrone-prostate". Such an aspect actually was found by ZUCKERMAN and GROOME (7) in one of nine dogs suffering from spontaneous hypertrophy of the prostate. If the testosterone level decreases only slightly the ability to temper the oestrone-hypertrophy is mainly or totally preserved and a hypertrophy of the prostate does hardly or not occur.

Summary.

In a series of 13 male dogs, in which the influence of varying quantities of oestrone, testosterone and their combinations upon the weight and the histological picture of the prostatic gland was investigated the following was found:

1. A certain quantity of testosterone, together with oestrone, gives rise to a beginning differentiation of the epithelium which fails in case of each of the substances being given alone in the same dose.
2. This quantity of testosterone alone does not cause any growth of the prostata. It inhibits, but only very partially, the rank growth induced by oestrone, so that still a pathological hypertrophy remains.

Herewith the main difference between the spontaneous prostatic hypertrophy and the oestrone hypertrophy of the castrate is taken away and a new corroboration is furnished for the view that the hypertrophy of the prostatic gland is due to a "dysorchidy", consisting of a relative change of the equilibrium male hormone-„oestrone-like substance", in favour of the latter.

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