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Received May 18, 1954. P.S.E.B.M., 1954, v86.

Physiological Action of 19-Norprogesterone in the Guinea Pig. (21129)

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Progesterone is the most potent antifibromatogen(1,2). However, there is no concomitant increase of the antifibromatogenic potency of testosterone when its progestational activity is increased by substitutions at C_{17} as with ethinyl-testosterone(3,4). Likewise, this progestational compound has no concomitant faculty to antagonize the hysterotrophic(3) or luteinizing action of estrogen (5).

It was of especial interest to examine whether the 3 mentioned actions (antifibromatogenic, antihysterotrophic, luteinizing) will increase with the progestational potency of derivatives of progesterone such as Δ^{11}-dehydroprogesterone(6) and 19-norprogesterone(7). The first of these compounds is 3 times, the second one 4 to 8 times as progestational as progesterone(6,8).

In a group of 30 animals we have found that Δ^{11}-dehydroprogesterone (Δ^{11}-dehydro-P) shares with progesterone (P) its antifibromatogenic and antihysterotrophic activity(9). But it is not certain whether antifibromatogenic potency of Δ^{11}-dehydro-P is greater than that of P; individual variations of the fibrous tumoral reaction in similar experiments and the error in calculation of quantities absorbed from subcutaneously implanted pellets especially when working with small quantities are considerable(10,11). The antihysterotrophic action of Δ^{11}-dehydro-P was certainly not greater than that of P. As we shall see the same result was obtained in new experiments. So far, we have not made a comparative study of the antiluteinizing potency of this compound.

Experiments. A group of castrated female guinea pigs were implanted subcutaneously with pellets of estradiol and Δ^{11}-dehydro-P, and another group with pellets of estradiol and 19-nor-P. In some experiments the pellets contained 40% of the specific steroid mixed with cholesterol, in others only 20%. This procedure, formerly used in experiments with P, assures absorption of very small amounts of the specific steroid. Classification of the fibrotumoral reaction was done as described previously(12).

Comparative results with P, Δ^{11}-dehydro-P, and 19-nor-P are given in Table I. This table shows that with Δ^{11}-dehydro-P the estrogen-induced fibrous effect is counteracted as with P. But, as found previously, with Δ^{11}-dehydro-P the antifibromatogenic activity was not strikingly superior to that of P (compare IV to II, and V to III); the difference was probably in the limit of the error (variation of the fibrous tumoral reaction; calculation of quantities absorbed). As to the antihysterotrophic activity Δ^{11}-dehydro-P was not superior to P.

With 19-nor-P both the antifibromatogenic and antihysterotrophic activity were considerably greater than those of P (compare VII to III).

The antiluteinizing activity of P can be expressed in the quantity necessary to counteract the luteinizing action of estrogen in intrasplenic grafts(5). With 16 to 23 μg per day absorbed from a 40% progesterone-cholesterol pellet frequency of corpora lutea is reduced

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TABLE I. Comparative Antifibromatogenic and Antihysterotrophic Activity of 3 Progestational Compounds in Guinea Pigs with Subcutaneously Implanted Pellets of Estradiol. Duration of experiments, 3 mo.

	Progestational steroid	No. of animals	Estradiol /day, μg	Progest. ster./day, μg	Fibrous tumoral effect†	Tumoral coeff. $Q_{2.3}$†	Uter. wt, g	Source of specific steroid No. of pellets, and percentage
I	Progesterone*	12	43	32 (21–47)	1.4 (.5–1.5)	0	2.1 (.9–2.7)	½–1, 40%
II	" *	16	37	15 (13–19)	1.4 (1 –1.5)	0	2.8 (1.7–5.1)	
III	" *	12	40	9 (5–12)	3.6 (1.5–8)	1.0	3.2 (1.9–5.2)	
IV	Δ^{11}-dehydroprog.	4	44	14 (13–16)	2.0 (1.5–3)	.25	3.9 (3.1–4.5)	2, 40%
V	"	16	54	8 (5–11)	2.6 (1.5–5.5)	.44	3.2 (1.9–5.1)	½–2, 40%
VI	"	4	51	4 (3– 4)	2.6 (1.5–4)	.5	3.9 (2.7–6.4)	½, 40%
VII	19-norprog.	23	44	7.4(5–12)	1.6 (1 –3)	.1	1.5 (1 –3.3)	1–2, 20%; ½, 40%
VIII	"	8	56	3.4(3– 4)	1.5 (1 –3)	.1	1.7 (1 –2.4)	½, 20%

* Former experiments; for comparison only. See (9) and (13); with small corrections.
† Tumors of class 2 and 3. See for explanation (12).

from 90 to as little as 30%. In the present work with 12 to 23 μg of 19-nor-P per day absorbed from a similar pellet there was in 10 animals none with corpora lutea.

Discussion. Our comparative work with the 3 progestational compounds leaves no doubt that 19-nor-P is superior to P as to antifibromatogenic, antihysterotrophic, and antiluteinizing activity. Since as previously known, 19-nor-P is 4 to 8 times as progestational as P(8), 19-nor-P is superior to the latter is no less than 4 different functional aspects.

P also protects against toxic actions of estrogen, such as uterine bleeding and necrosis, which have been observed in guinea pigs receiving estrogen for several months(1;2, p. 118). Both Δ^{11}-dehydro-P and 19-nor-P have probably even greater capacity in this respect than P. In Group II with progesterone there were 2 cases with uterine necrosis; there was no uterine necrosis with Δ^{11}-dehydro-P or 19-nor-P.

On the basis of actual experimental knowledge one may reasonably ask why our body is using P and not 19-nor-P in matters of steroid homeostasis. One may venture that biosynthesis of 19-nor-P in ovarian structures would have been as easy as that of P.

As previously reported, calculation of absorption is subject to considerable error (10,11), particularly as calculation in the present work was based on the assumption that with 19-nor-P there was non-selective absorption from mixed pellets, as with P and those steroids for which non-selective absorption has been established(13-15). But our conclusion as to the high antifibromatogenic and antihysterotrophic activity of 19-nor-P remains unshaken even should we admit for this compound exceptionally selective absorption. Thus, in Group VIII the average weight of the pellet containing but 20% of 19-nor-P was 12.2 mg (range: 8.3-17.6). With selective absorption a maximum of 2.4 mg of 19-nor-P could have been absorbed in the course of 90 days, or 27 μg per day; an antifibromatogenic and antihysterotrophic action was obtained which was not inferior to that obtained with 21 to 47 μg of P in Group I.

Several years ago progesterone was unsuc-

cessfully used against uterine fibromyoma in women(16), possibly due to insufficient quantities of progesterone absorbed(2; p. 167). We feel that it would be of interest to repeat these clinical trials with 19-nor-P instead of P. Absorption from 19-nor-P pellets (pure, not mixed with cholesterol) is probably more rapid than from P pellets.

Summary. Antiestrogenic activities—antifibromatogenic, antihysterotrophic, antiluteinizing—of 19-norprogesterone have been compared to those of progesterone. 19-Norprogesterone, whose progestational activity is considerably greater than that of progesterone, is also strikingly superior as to antifibromatogenic, antihysterotrophic, and antiluteinizing action. On the contrary, the greater progestational potency of Δ^{11}-dehydroprogesterone compared to that of progesterone is seemingly not concomitant with greater antifibromatogenic and antihysterotrophic actions. The theoretical and practical bearings of the statements with 19-norprogesterone are discussed.

Thanks are due to Messrs. Syntex, México, for 19-norprogesterone, and to Messrs. Ciba, Basel, Switzerland, for Δ^{11}-dehydroprogesterone.

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Received May 19, 1954. P.S.E.B.M., 1954, v86.

Rauwolfia serpentina in Hypertensive Vascular Disease.*† (21130)

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In recent years, alkaloids of *Rauwolfia serpentina* have been found capable of producing hypotensive and sedative effects and bradycardia in animals and man. *Rauwolfia serpentina* (*Ophioxylon serpentinum*) is a tropical shrub growing throughout the Indian peninsula, the roots of which have been used for centuries for medicinal purposes. The hypotensive properties of the alkaloidal base extracted from this plant have been known since 1931(1), but clinical trials in hypertensive patients in this country were not carried out until a few years ago(2).

The present study was undertaken to throw further light on the clinical, circulatory and metabolic effects of *Rauwolfia serpentina* (Raudixin, Squibb) administered to patients

* This study was supported by grants from the Squibb Institute for Medical Research and the Irwin Strasburger Memorial Medical Foundation.

† The assistance of Drs. Stanley E. Bradley and Burton Cominsky in the catheter studies, and of Margaret Crymble, Iva Moen, Mary Iles and Margaret N. Hawthorne is gratefully acknowledged.