16557

Comparative Cortical Action of Different Pregnenolones in the Adrenalectomized Guinea Pig.

SILVIO BRUZZONE AND HUGO LOPEZ. (Introduced by A. Lipschutz.)

From the Department of Experimental Medicine, National Health Service of the Republic of Chile, Santiago.

The adrenalectomized rat,[1,2] dog,[3] and guinea pig[4] can be kept alive for a certain time with 21-acetoxypregnenolone (abbreviated 21-AOP; Δ^5 pregnene-3,21-diol-20-one-21 acetate). In the present work additional results with 21-AOP and results with 2 other compounds will be given: with pregnenolone (abbreviated P; Δ^5-pregnene-3-ol-20-one and its 3-acetate (abbreviated 3-AP). The compound P has been found to be active in the adrenalectomized rat by Selye,[1] but not by Segaloff and Nelson.[2] The second compound 3-AP has so far not been used in adrenalectomized animals.

Experiments. Ablation of the adrenals has been carried out in 2 stages by the technique we have described previously.[4] Pellets of the steroids were implanted subcutaneously after completion of the ablation of the second adrenal. It was necessary to implant 10 to 25 pellets so as to obtain absorption of sufficient quantities. Results with P and 3-AP are summarized in Table I. Experiments with 21-AOP (18 animals from our former work[4] and 7 new animals) are included for comparison. Animals which died within 2 days after the second stage of operation are not included; neither were animals in which an adrenal fragment was found at necropsy.

Adrenalectomized guinea pigs receiving no steroid seldom survive more than 7 days and rarely for 9. As seen from the table, with P only one animal survived for 9 days. On the other hand, with 21-AOP no less than 80% survived for more than 9 days. Animals receiving 3 AP occupy an intermediate position; several animals survived from 9 to 19 days. This was not due to the greater quantities of 3-AP administered since in 3 out of the 6 surviving animals there was absorption of 906 to 1060 μg per day, *i.e.* still in the range of the experiments with P and 21-AOP. There was loss of weight in all the 3 groups.

Our findings with P show that as much as 1.5 mg per day, *i.e.* a quantity twice that of 21-AOP did not prolong the survival of our guinea pigs. This corroborates the former findings with P in the rat.[2] Though P has had no influence on survival of the animals there was apparently some beneficial action. In this group no premortal convulsions have been observed as is the rule in guinea pigs dying from adrenal insufficiency. Though convulsions may have been overlooked, no hyperextension of the extremities was observed in these dead animals as is frequently the case with dead untreated animals.

A comparison between the groups receiving 21-AOP and 3-AP respectively is of considerable interest. There is, first, the remarkable difference as to the percentage of survival. Secondly, the maximal length of survival with 21-AOP was greater than with 3-AP. Third, the loss of weight was less pronounced with 21-AOP than with 3-AP. Fourth, with 21-AOP the chance of survival increased with greater quantities administered; on the contrary, as already stated, with 3-AP there was apparently no greater chance of survival when greater quantities were given.

Our comparative results show that 3-AP is a very poor substitute for cortical ste-

1 Selye, H., *Science*, 1941, **94**, 94.

2 Segaloff, A., and Nelson, W. O., *Endocrinology*, 1942, **31**, 592.

3 Cleghorn, A. R., *Endocrinology*, 1943, **32**, 165.

4 Bruzzone, S., Borel, H., and Schwarz, J., *Endocrinology*, 1946, **39**, 194.

TABLE I.
Fifty-seven Adrenalectomized Guinea Pigs with Subcutaneously Implanted Tablets of 3 Different Pregnenolones.

Steroid	Absorbed per day, μg	No. of animals	No. of animals dying on days indicated			% of animals surviving for more than 9 days	Longest survival, days	Loss of wt per day
			2-7	8-9	>9			
Pregn.	716-1466	10	9	1	0	0	9	113
3-acetate	733-2625	22	14	2	6	27	19	140
21-acetoxy	700-1250	25	5	0	20	80	162	65

Prgn. M.P. = 190°; 3-acet. preg. M.P. = 149-150°; 21-acetoxy-pregn. M.P. = 183°.

roids. But since 3-AP is more active than P one wonders whether the cortical action of 21-AOP might be further increased by esterification at C_3 also, *i.e.* using a diester of 21-oxypregnenolone.

Summary. Pregnenolone was unable to keep alive the adrenalectomized guinea pig. There was some cortical activity with 3-acetate-pregnenolone. But the activity of 3-acetate of pregnenolone was much less than that of 21-acetoxypregnenolone.*

* Our thanks are due to Dr. E. Oppenheimer, Ciba Pharmaceutical Products, Summit, N.J., and Dr. Carl Miescher, Ciba, Basel, for a generous supply of steroids.

16558

On the Antitumorigenic Action of Large Quantities of Pregnenolones.

RIGOBERTO IGLESIAS AND SILVIO BRUZZONE. (Introduced by A. Lipschutz.)
From the Department of Experimental Medicine, National Health Service of the Republic of Chile, Santiago.

Estrogen-induced abdominal fibroids can be prevented by different 3-keto-steroids,[1] of which progesterone is the most powerful.[2] But the original supposition that there is a correlation between progestational and antifibromatogenic action[2,3] had to be discarded when it was shown that enhancement of progestational activity by a substitution at C_{17} is not accompanied by an increase of antifibromatogenic activity; ethinyl- and ethyltestosterone are even less antifibromatogenic that testosterone.[4,5]

So far no steroid with an hydroxyl group at C_3 has been found to be antifibromatogenic; neither 21-acetoxypregnenolone (abbreviated 21-AOP),[3] nor 3-acetate-pregnenolone (abbreviated 3-AP)[6] prevented estrogen-induced fibroids even when quantities several times larger than those of progesterone were used. On the other hand, pregnenolone derivatives may show unexpected activity when administered in very large quantities; progestational[7] and cortical activity[8,9,10] and protective action on the sem-

1 Lipschutz, A., *Nature* (Lond.), 1944, **153**, 260; *Experientia* (Basel), 1946, **2**; *Bull. Acad. Méd.* (Paris), 1947, 229.

2 Lipschutz, A., Bruzzone, S., and Fuenzalida, F., *Cancer Research*, 1944, **4**, 179.

3 Lipschutz, A., Bruzzone, S., and Fuenzalida, F., PROC. SOC. EXP. BIOL. AND MED., 1943, **54**, 303.

4 Iglesias, R., and Lipschutz, A., *Lancet*, 1946, **2**, 488.

5 Lipschutz, A., Iglesias, R., Bruzzone, S., Fuenzalida, F., and Riesco, A., *Fourth Internat. Cancer Research Congress*, 1947, 23; *Texas Reports of Biology and Medicine*, 1948, in publication.

6 Iglesias, R., unpublished work; see series LXXXI in Table I of the present paper.

7 Selye, H., and Masson, G., *J. Pharm. and Exp. Therap.*, 1943, **77**, 3.

8 Selye, H., *Science*, 1941, **94**, 94.