

except that angiotonin is reported to cause a reduction in cardiac output when measured by the ballistocardiographic method.<sup>9, 10</sup> The acute pressor effect of renin differs from that of adrenalin in its failure to increase the cardiac output, basal metabolic rate<sup>18</sup> and forearm flow. In these respects the action of renin is similar to that of paredrinol<sup>19</sup> but renin produces a more marked decrease in the blood flow of the hand than does paredrinol. The acute effect of renin differs from chronic hypertension in man both by the elevation of venous pressure and the decrease in blood flow in the hand.<sup>20</sup>

## 13439

### Duality of Pituitary Gonadotrophins. Effects of FSH-ICSH Mixture on Hypophysectomized Male and Female Rats.\*

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The dual nature of the gonadotrophins of pig and sheep pituitaries has been demonstrated beyond question by the preparation of pure ICSH<sup>† 1, 2, 3</sup> (interstitial cell stimulating or luteinizing hormone) and very active<sup>4, 5, 6</sup> or biologically pure<sup>7, 8</sup> FSH<sup>†</sup> (follicle-stimulat-

<sup>18</sup> Grollman, A., *The Cardiac Output of Man in Health and Disease*, Chas. C. Thomas, 1932.

<sup>19</sup> Stead, E. A., Jr., and Kunkel, P., *J. Clin. Invest.*, 1939, **18**, 439.

<sup>20</sup> Weiss, S., Publication No. 13, *Blood, Heart and Circulation*, Am. Assn. Adv. Sci., 1940, p. 295.

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† The use of names which clearly indicate a function of a hormone such as follicle stimulating (FSH) or gametotropic on the one side and interstitial cell stimulating (ICSH) or hormonotrophic on the other appears to us preferable to the coinage of a new nomenclature.

<sup>1</sup> Shedlovsky, T., Rothen, A., Greep, R. O., Van Dyke, H. B., and Chow, B. F., *Science*, 1940, **92**, 178.

<sup>2</sup> Li, C. H., Simpson, M. E., and Evans, H. M., *Endocrinology*, 1940, **27**, 803.

<sup>3</sup> Li, C. H., Simpson, M. E., and Evans, H. M., *Science*, 1940, **92**, 355.

<sup>4</sup> Fraenkel-Conrat, H., Simpson, M. E., and Evans, H. M., *Anales de la Facultad de Medicina* (Montevideo), 1940, **24**, No. 5, 6, 7, 8.

<sup>5</sup> Fraenkel-Conrat, H., and Simpson, M. E., *Proc. Soc. Exp. Biol. and Med.*, 1940, **45**, 627.

<sup>6</sup> Jensen, H., Tolksdorf, S., and Bauman, F., *J. Biol. Chem.*, 1940, **135**, 791.

<sup>7</sup> Greep, R. O., Van Dyke, H. B., and Chow, B. F., *J. Biol. Chem.*, 1940, **133**, 289.

<sup>8</sup> McShan, W. H., and Meyer, R. K., *J. Biol. Chem.*, 1940, **135**, 473.

ing hormone) from both sources. The results of certain parabiotic experiments, however, have in the opinion of some authors cast doubt on the *secretion* of two gonadotrophins by the pituitary.<sup>9</sup>

The most clear-cut of these experiments was performed by Greep.<sup>10</sup> He united parabiotically with a castrate male both a hypophysectomized male and female rat and thus was able to observe the effects of the same pituitary acting simultaneously on the male and female gonads and accessories. He noted follicular and uterine development in the female, and testis and accessory enlargement in the male parabiont. This has been looked upon as evidence for the view that only one hormone is actually secreted by the pituitary which in this case showed the properties attributed to FSH in the female and to ICSH in the male rat.

Known differences in the reactivity of the two sexes to the two pituitary gonadotrophins appeared to us to amply account for the results of such parabiotic experiments. The effort was hence made to demonstrate that these diverse effects on a male and a female parabiont could be reproduced by administering the same mixture of the two purified gonadotrophins to hypophysectomized males and females.

A mixture of 0.5 units of FSH and 0.5 units of ICSH therefore was injected subcutaneously daily for 4 days to 2-day post-operative 23-day-old hypophysectomized male and female rats, with autopsies on the 5th day, 24 hours after the last injection. As indicated in Table I, testis and ventral prostate enlargement<sup>‡</sup> were evident in the male rats, while follicular development and estrous uteri but no corpora lutea occurred in the females.<sup>§</sup> It has thus been shown that

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<sup>9</sup> Smith, P. E., *Univ. of Pennsylvania Bicentennial Conference*, 1941, 19-31.

<sup>10</sup> Greep, R. O., *PROC. SOC. EXP. BIOL. AND MED.*, 1940, **44**, 214.

<sup>‡</sup> Confirming the interesting discovery of Greep *et al.*,<sup>11</sup> we find the ventral prostate of the 2-day postoperative, 23-day-old rat very much more sensitive as an indication of the action of ICSH than any other part of the male accessories, such as the seminal vesicles.<sup>12</sup> This type of rat has therefore been routinely used for the assay of ICSH and for that reason also in these experiments.

<sup>11</sup> Greep, R. O., Van Dyke, H. B., and Chow, B. F., *PROC. SOC. EXP. BIOL. AND MED.*, 1941, **46**, 644.

<sup>12</sup> Fraenkel-Conrat, H., Li, C. H., Simpson, M. E., and Evans, H. M., *Endocrinology*, 1940, **27**, 793.

<sup>§</sup> Histological examination of the ovaries of rats receiving the two gonadotrophins also revealed only follicles with no signs of luteinization. The interstitial tissue, which in controls of both sexes does not show fargoing regression during this short postoperative period, did not appear appreciably stimulated by the ICSH alone or in combination with the FSH. This is in accord with previous findings that somewhat smaller amounts of ICSH can be detected, on subcutaneous injection, by its augmenting effect on the FSH, in the female, than are needed for repair or

TABLE I.  
Weights of Gonads and Accessories of Hypophysectomized Male and Female Rats\*  
Injected with FSH and ICSH†

| Hormones   | No. of rats |    | Males            |                            |                            | Females        |                 |
|------------|-------------|----|------------------|----------------------------|----------------------------|----------------|-----------------|
|            |             |    | Testes,<br>mg    | Ventral<br>prostate,<br>mg | Seminal<br>vesicles,<br>mg | Ovaries,<br>mg | Uterus,<br>mg   |
|            | ♂           | ♀  |                  |                            |                            |                |                 |
| FSH + ICSH | 9           | 10 | 224<br>(195-280) | 13<br>(10-15)              | 7<br>(4-10)                | 24‡<br>(13-31) | 80‡<br>(53-103) |
| FSH alone  | 5           | 3  | 242<br>(236-249) | 8<br>(6-8)                 | 7<br>(6-8)                 | 12<br>(10-14)  | 22<br>(18-28)   |
| ICSH alone | 5           | 4  | 130<br>(118-154) | 12<br>(10-15)              | 8<br>(5-11)                | 10<br>(6-12)   | 21<br>(20-22)   |
| Controls   | 4           | 3  | 117<br>(103-124) | 8<br>(7-8)                 | 7<br>(6-9)                 | 9<br>(8-10)    | 24<br>(20-31)   |

\*23 days old, 2 days p.o. at onset of injections, injected subcutaneously daily for 4 days, with autopsies on 5th day.

†A total dose of 2 units was given of each hormone, with the exception of the group of males receiving FSH alone, in which the dose was doubled to test for ICSH contamination. Units were determined in the usual 3-day test in 6-8 day post-operative rats, 26-28 days old at operation.<sup>1,4</sup> Both preparations used contained 80 units per mg. The ICSH contained less than 0.1% FSH; the FSH about 10% ICSH.

‡Medium to medium large follicles, no luteinization; estrous uterus in 7 rats. No follicular or uterine stimulation in the other groups.

an artificial mixture of the two sheep gonadotrophins will be follicle-stimulating in its action on the female, while in the male it stimulates the interstitial tissue to secrete androgens. The logical interpretation of these findings appears to be that there is a difference in the responsiveness of the two sexes to the two hormones: the female being more sensitive to the FSH, the male to the ICSH. Nevertheless the presence of the ICSH is evident also in the female (in our as well as in Greep's experiment), by its augmentation of the follicular-stimulating effect of the FSH and by the production of estrogens, now believed to be due to the synergism of the two hormones.<sup>12, 13, 3</sup> Conversely, the presence of the FSH also documents itself in the male by the considerable enlargement of the testes which is far greater than that produced by the ICSH alone.¶

This response of the two sexes to the same gonadotrophic stimulation of the interstitial tissue. Similarly the FSH alone showed no activity at this level and in this type of rat, while assays in the usual type of hypophysectomized rat showed the indicated potency.

<sup>13</sup> Fevold, H. L., *Endocrinology*, 1940, **26**, 999.

¶ The effect is additive; no augmentation of testis or accessory weights was observed in this nor in many other experiments in which both FSH and ICSH were given to hypophysectomized male rats.

ture resembles qualitatively, though obviously not quantitatively, that noted by Greep in his male and female parabionts, both under the stimulation of one pituitary. Parabiotic studies can thus not be regarded as evidence concerning the number of gonadotrophins secreted by the pituitary. Such evidence can be obtained only from the isolation of the pure hormones from the blood as it has been done from the pituitary.

*Summary.* A mixture of purified FSH and ICSH was shown to produce predominantly follicle-stimulating effects in female and interstitial cell-stimulating effects in male hypophysectomized rats. These differences in the response of the two sexes were secured by the simultaneous administration of both hormones and it would consequently not seem valid to interpret such phenomena as evidence for the existence of a single pituitary gonadotrophin.

## 13440 P

### Nitrogen Balance in Experimental Tryptophane Deficiency in Man.\*

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The observations here reported comprise a part of a more comprehensive study undertaken jointly by the Departments of Medicine and Pediatrics of the Johns Hopkins University on experimental amino acid deficiencies in man. The purpose of this study was twofold. It was felt desirable to determine human amino acid requirements by direct observations on man, rather than by inferences based on animal experiments, since it is now known that even closely related animal species differ in their amino acid requirements. A second purpose was to discover whether deficiencies of particular amino acids produced characteristic pathological changes which could be recognized by clinical or laboratory technics. It seemed probable that, in certain parts of the world at least, specific amino acid deficiencies might be present, and that a familiarity with the picture,

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