Prolactin secretion in infertile men before and after treatment with bromocriptine

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Summary.   This report studies prolactin secretion in infertile men and the effect of bromocriptine treatment.

Twelve normal and 90 infertile men are studied. Prolactin, LH, FSH and testosterone are specifically radioimmunoassayed, and urinary androgens determined by gas chromatography. Spermatogenesis is determined using spermocytograms or by testis biopsy ; LH-RH and TRH tests are used. In the second part of the study, 18 infertile men having high prolactin levels are treated with bromocriptine for one month (5 mg/day), and the above tests repeated during the treatment.

Using spermograms and the LH-RH test, the patients are divided into the following groups : control (1), normogonadotropics (2), hypogonadotropics with lower titers of LH and/or FSH (3), hypergonadotropics with LH (and sometimes FSH) response to LH-RH greater than normal with normal or slightly higher basic levels (4), azoopermia with no spermatogenesis (5).

Prolactin secretion and correlation with gonadotropins and androgens. Prolactin secretion is higher before or after TRH in 40 p. 100 of infertile men. There seems to be a correlation between gonadotropins and prolactin ; this result provides additional evidence that there is no antagonism between prolactin and gonadotropin secretion in man. Prolactin secretion is frequently correlated with plasma testosterone or urinary androgens. However, this correlation is negative when spermatogenesis is blocked before the spermatocyte stage.

Results obtained during treatment with bromocriptine. Prolactin secretion, basal levels and response to TRH are reduced. At the same time, basic FSH and LH increase and androgens decrease, but these modifications are slight and the range of individual variation is wide. The number of spermatozoa also increases considerably (15 to 31 × 10^6/ml). This result suggests that hyperprolactinemia interfers with the final stages of spermatogenesis and that bromocriptine treatment leads to resumption of normal gonadic function.

Introduction.

Prolactin has been isolated in man and defined as an antepituitary hormone, different from the growth hormone (Guyda, Hwang and Friesen, 1971 ; Lewis *et al.*,

1971). Specific radioimmunological determination (Hwang et al., 1971) enabled us to undertake the physiopathological study of prolactin secretion.

It rapidly became evident that, due to a plasmatic half-life of about 15 min, a circadian rhythm (Nokin et al., 1972) and the effect of stress (sometimes considerable) (Noel et al., 1972), the interpretation of an isolated prolactinemia value was hazardous. It was thus necessary to carry out dynamic tests to estimate the stimulation or inhibition of secretion ; these tests used either TRH (thyrotropin-releasing hormone), known to release prolactin (Bowers et al., 1973 ; Jacobs et al., 1971), or rye ergot derivatives such as bromocriptine which inhibits prolactin secretion (Besser et al., 1972 ; Del Pozo et al., 1972).

The relationships between prolactin secretion and the male gonadic function are not yet well known, especially in man ; however, some studies suggest that prolactin has a stimulatory effect. According to these, prolactin would increase the testosterone secretion (Rubin et al., 1975), and an induced hyperprolactinemia would be accompanied by testosterone response, greater after stimulation by HCG (Ambrosi et al., 1976).

On the other hand, contrasting results favor an inhibitory effect. The majority of hyperprolactinemic patients are hypogonadic or impotent (Boyar et al., 1974 ; Thorner et al., 1974 ; Fossati, Strauch and Tourniaire, 1976) ; induced hyperprolactinemia is followed by lower DHT response after stimulation by HCG (Magrini et al., 1976) and induced hypoprolactinemia is accompanied by increased testosterone secretion after HCG (Besser and Thorner, 1975).

Given these apparently contradictory results, the aim of this report is to study prolactin secretion in normal and infertile men, and to determine the consequences of curbing prolactin secretion with bromocriptine.

Material and methods.

1. *Patients.*

One hundred and two men (12 controls and 90 sterile subjects), between 20 and 38 years of age, were thoroughly examined. The 90 sterile patients were married and had been for at least three years ; the normal functioning of the hypothalamo-pituitary-ovarian activity of their wives had been checked. The patients did not present any hepatic or renal malfunction nor any visible signs of pituitary tumor. After clinical examination, they underwent biological evaluation, including one or two spermocytograms, a spermoculture to look for possible genital infection, a thermograph of the scrotum to discover eventual varicocele, a karyotype, static and dynamic hormonal studies of urine and plasma represented by LH-RH and TRH tests, and a bilateral testis biopsy for the cases of azoospermia or severe oligospermia.

2. *Classification for study of prolactin secretion* (table 1).

The 102 patients examined were selected from a larger group of infertile patients, a detailed study of which is published elsewhere (Boucher et al., 1977).

Controls : Twelve men, 20 to 35 years old, with at least one child, and presenting no known or discernible disease.

TABLE 1

Gonadotropinemia (mUI/ml), before and after 50 µg of LHRH in infertile men (mean ± SEM)

	Controls	Moderate oligospermia or excretory azoospermia				Azoo- or important secretory oligo-spermia with spermatogenesis arrest		
		normo-gonadotropics	hypo-gonadotropics I	hypo-gonadotropics II	hyper-gonadotropics	spermatocyte II spermatid I	spermatogonia spermatocyte I II	no spermatogenesis III
n	12	38	21	12	27	19	11	10
FSH (basal)	6.9 ± 0.6	6.3 ± 0.4	2.5 ± 0.5	4.8 ± 0.6	8.8 ± 1.6	14.1 ± 1.1 *	22.5 ± 2.3 *	57.7 ± 11.1 *
FM	11.8 ± 1.2	10.6 ± 0.6	6.1 ± 0.9	6.6 ± 0.5	20.1 ± 2.7 *	26.4 ± 1.6 *	50.4 ± 1.4 *	118.8 ± 11.4 *
LH (basal).	3.8 ± 0.3	4.9 ± 0.3	3.1 ± 0.3	4.5 ± 0.6	5.4 ± 0.7	5.2 ± 0.6	5.4 ± 0.6	7.6 ± 1.7 *
LM	14.4 ± 1.0	15.1 ± 0.6	8.6 ± 0.6	9.0 ± 0.7	35.3 ± 6.4 *	22.2 ± 2.4 *	25.2 ± 2.5 *	34.9 ± 6.6 *
FM/LM	0.87 ± 0.13	0.74 ± 0.05	0.89 ± 0.25	0.79 ± 0.09	0.63 ± 0.09	1.38 ± 0.14 *	2.25 ± 0.28 *	4.11 ± 0.58 *

n : Number of subjects.
FM-LM : Maximum values of FSH and LH after 50 µg of LHRH.
* : Statistically different than the controls, $p < 0.05$.

Cases of oligospermia or excretory azoospermia : These patients did not present large blockage of spermatogenesis. This group includes excretory azoospermia, oligozoospermia (2 to 40 $\times$ 10^6 spermatozoa/ml), asthenospermia (motility lower than 70 p. 100 1 hour after emission), teratospermia (number of abnormal forms higher than 40 p. 100) and cases of idiopathic sterility. They were divided into four sub-groups, according to the character of LH and FSH secretion before and after LH-RH :

Normogonadotropics : normal FSH and LH secretion,
Hypogonadotropics I : low basal LH or FSH levels,
Hypogonadotropics II : normal basal level, low response to LH-RH,
Hypergonadotropics : normal or sligthly high levels, exaggerated response to
                          LH and sometimes to FSH.

Cases of severe secretory azoo- or oligospermia : These patients presented spermatogenetic blockage ; they constitute three groups according to degree of blockage :

Azoospermia   I : blockage at spermatocyte II or spermatid stage,
Azoospermia II : blockage at spermatogonia or spermatocyte I stage,
Azoospermia III : Sertoli cells only, Klinefelter syndrome (XXY), bilateral cryptochidia.

3. *Bromocriptine treatment* (CB 154 from Sandoz Laboratories).

Eighteen oligospermic infertile subjects with exaggerated prolactin secretion (basal level PO > 300 μU/ml) in response to stimulation by TRH (ΔP > 800 μU/ml) were treated with bromocriptine for a period of 30 days at a dose of 5 mg/day (1 tablet morning and evening). Between day 25 and day 30 of treatment, they were completely examined : spermocytogram, urinary and plasma hormones, LH-RH and TRH tests. This preliminary examination after the beginning of the treatment was designed to reveal any possible spermiogenetic activity, and mainly to interrupt the treatment which could prove harmful.

4. *Analytical methods.*

a) *The spermatograms* included determination of spermatozoon number and motility and spermatozoon morphology, using the classification proposed by David *et al.*, 1975).

b) *Hormonal examination* of urine was carried out on the urine collected over 24 hours. The 17 hydroxysteroids and the 17 cetosteroids were assayed by the colorimetric method. Androsterone, etiocholanolone and dihydroepiandrosterone were assayed by gas chromatography on a Packard 7 400 chromatograph : flame ionization detector at 290 °C, injection chamber at 280 °C, a glass column containing an OV1 1 p. 100 phase, temperature programmed at 1 °C/min from 210 to 270 °C, internal epicoprostanol standard. Urinary FSH and LH were assayed by immunochemical method with luteonosticon and FSH-nosticon reactives from the Organon Laboratories.

c) *Plasma assay* of testerone, FSH, LH and prolactin was carried out by radioimmunological methods. Blood samples were taken in the morning between 8: 30 and 9 : 00.

Testosterone assay was done after adsorption on coal-dextran and the results expressed in ng/ml.

The method used for the FSH was that of « double antibody » with the second antibody fixed on activated cellulose. The standard was a MRC 68/39 preparation (immunological equivalent : 2,830 IU per mg ; biological activity : 3,500 IU per mg). The results are expressed in mlU/ml, 1 mlU = 0.353 ng.

The method for LH was identical to that used for FSH. The MRC 68/40 preparation constituted the standard, its immunological equivalent being 2,160 IU per mg of LH, and its biological activity 2,000 IU IRP2 per 1 mg. The results are expressed in mlU/ml, 1 mlU = 0.463 ng.

The reference standard for prolactin was a MRC 71/222 ; the immunological equivalent is 40 IU per 1 mg of prolactin supplied by the NIH (NIH-V-L-S = 1). The results are expressed in μU/ml, 1 μU = 0.025 ng.

d) *The dynamic examination* included a LH-RH test and a TRH test carried out simultaneously, according to the modalities described in detail elsewhere (Boucher, 1976). The tests were done between 8 : 30 and 12 : 30 p.m. on an empty stomach. An intravenous catheter was placed 20 min before the beginning of the test. 50 μg synthetic LH-RH (Stimu-LH, Roussel) and 200 μg TRH (Laboratories Roche) were quickly injected intravenously at 0 hour. The blood samples were immediately centrifuged and the plasma stored at —20 ºC. FSH and LH were assayed at 0, 10, 20, 30, 45, 60, 90, 120 and 150 min ; prolactin was assayed at 0, 30, 60 and 120 min. The results were analyzed, taking into particular consideration basal values (PO, LHO, FSHO) the highest levels after TRH or LH-RH stimulation (P30, LHM, FSHM), and the cumulative responses equal to the surfaces defined by the response curve and the straight line continuous to the basal level (SPRL, SLH, SFSH).

5. *Statistical analysis.*

The statistical study was done on a programmable Monroe calculator. Various data were compared using analysis of the variant. For some parameters, different correlations were studied statistically, i.e. determination of the correlation coefficient between two parameters (Snedecor and Cochran, 1967).

Results.

Prolactin secretion before and after TRH (table 2).

Twenty min after the intravenous catheter was placed, basal prolactin level was 226 $\pm$ 20 μU/ml in the controls. In the different groups of infertile subjects this basal value was higher, but the differences were non-significant, with the exception of the subjects presenting an arrest of spermatogenesis at spermatocycle II or spermatid stage.

Under our experimental conditions, and in all groups considered, the prolactin surge took place 30 min after intravenous injection of TRH. At 60 min, prolactinemia diminished, but still remained significantly higher than the basal level. However,

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TABLE 2

Prolactinemia (µU/ml) before and after 200 µg IV of TRH in infertile men (mean ± SEM)

Groups	Controls	Moderate oligospermia or excretory azoospermia				Azoo- or important secretory oligo-spermia with spermatogenesis arrest		
		normo-gonadotropics	hypo-gonadotropics I	hypo-gonadotropics II	hyper-gonadotropics	spermatocyte II spermatid I	spermatogonia spermatocyte I II	no spermatogenesis III
n	12	27	6	9	22	10	8	7
PRL0	226 ± 20	284 ± 51	298 ± 64	186 ± 42	259 ± 37	421 ± 80 *	259 ± 20	219 ± 83
PRL30 ...	751 ± 59	1 220 ± 260	1 157 ± 259	556 ± 113	1 544 ± 315	1 399 ± 175	1 300 ± 132	945 ± 255
PRL60 ...	410 ± 23	616 ± 98	618 ± 139	324 ± 64	687 ± 86	757 ± 49	869 ± 199 *	851 ± 257
PRL120 ..	220 ± 27	259 ± 38	315 ± 47	178 ± 38	351 ± 55	357 ± 49	310 ± 50	341 ± 182
ΔPRL.....	525 ± 51	996 ± 238	884 ± 217	370 ± 79	1 285 ± 305	1 051 ± 152	1 055 ± 130	908 ± 222
SPRL	0.23 ± 0.02	0.35 ± 0.06	0.46 ± 0.13	0.16 ± 0.04	0.44 ± 0.06 *	0.50 ± 0.08 *	0.54 ± 0.08 *	0.56 ± 0.20

n : Number of subjects.
PRL0-PRL30 : Prolactinemia at different times after TRH.
ΔPRL : Increase of prolactin between time 0 and 30 mn.
SPRL : Cumulative response after TRH.
* : Statistically different than the controls, $p < 0.05$

120 min after injection, the prolactin levels were not significantly different from the basal level.

We noted a significant correlation between the basal level (PO) and the surge after TRH (P30) in all of the infertile subjects (r = 0.598, p < 0.001) and also in the group of oligospermic-normogonadotropic subjects (r = 0.818, p < 0.001). In the same groups there is a significant relation between PO and the other criteria for estimating TRH-induced prolactin release (ΔP, SP). On the other hand, these correlations are not significant for the other groups when they are studied separately.

Generally, the relations between criteria used for estimating TRH prolactin release are significant, in particular P30-ΔP and SP. Only the percentage increase as compared to the basal level (ΔP/PO) was not correlated with the other parameters.

When compared to the controls, oligospermic hypogonadotropic (II) subjects presented lower but not statistically significant prolactin release after TRH. In all the other groups of infertile subjects, we noted an increase of prolactin surge, significant in the groups of oligospermic hypergonadotropics and also in the group of secretory azoospermic patients considered as a whole or taking into account the different degrees of spermatogenetic blockage. No differences were noted between the three groups of azoospermic patients.

The subjects in each group did not all present abnormal prolactin secretion. Before or after TRH, the criteria used (PO > 300 μU/ml or ΔP > 800 μU/ml) showed high prolactinemia in 50 p. 100 of the azoospermic or oligospermic hypergonadotropic subjects, in 25 p. 100 of the oligospermic normogonadotropic subjects and in 10 p. 100 of the oligospermic hypogonadotropics.

When the infertile patients were separated into three groups (PO < 80 μU/ml ; PO > 300 μU/ml ; 80 < PO < 300 μU/ml), FSH, LH and urinary androgens A + E (androsterone + etiocholanolone) were significantly higher before and after LH-RH in the groups where basal prolactinemia was greater than 300 μU/ml.

However, there seems to be no hypoprolactinemia in man. In fact, there is no difference in the parameters studied between groups PO < 80 μU/ml and 80 < PO < 300 μU/ml.

Correlations between prolactin and other hormones.

We systematically looked for correlation, within the various groups, between prolactin and other hormone secretions such as plasma testosterone, urinary androgens A + E and plasma FSH and LH.

Prolactin-androgens. In infertile subjects, there was a significant correlation between blood testosterone and urinary androgens. In the total number of infertile patients, we noted, on the one hand, a significant relation between basal prolactin and testosterone, and on the other, between basal prolactin and urinary androgens (A + E). When each group was considered separately, we frequently found the same correlations, particularly between prolactin and A + E. This correlation disappears in the oligospermia hypergonadotropic subjects, but becomes negative (P = 0.05) in the cases of very early blockage of spermatogenesis.

Prolactin-FSH. We have never observed any correlation between basal FSH and prolactin values. We did note, however, a significant relation between FSH response

after LH-RH and prolactin response after TRH in control subjects (SF-P30, r = 0.817) oligospermic normogonadotropics (SF-P30, r = 0.408) and hypogonadotropics (SF-SP, r = 0.953). A significant negative correlation appeared between basal prolactin levels and FSH surge after LH-RH in azoospermics (PO-SF, r = 0.536) and oligospermic hypergonadotropics (PO-FM, r = 0.505).

Prolactin-LH. There was no evidence of a close relation between basal prolactin and LH secretions, although we had noted a hardly significant correlation (P = 0.05) in oligospermic hypergonadotropics (PO-LO, r = 0.478). We observed a significant correlation between prolactin and LH surge after TRH and LH-RH, respectively, in controls (P30-SL, r = 0.712) and azoospermics (SP-SL, r = 0.460).

Prolactin-FSH/LH. In cases of spermatogenetic arrest at spermatocyte I stage, the surge of PRL after TRH corresponds significantly to the basal level of FSH/LH before (FO/LO, r = 0.842) and after (FM/LM, r = 0.828) LH-RH stimulation. There also appears to be a hardly significant relation in oligospermic hypohypergonadotropics.

Bromocriptine treatment (table 3).

Eighteen infertile men presenting high prolactin levels before or after TRH were treated for one month with bromocriptine (5 mg/day). Examination between the days 25 and 30 of treatment gave the following results :

Effect on prolactin secretion (fig. 1).

Treatment was followed by a definite decrease in prolactin secretion which became inferior to the controls before and after TRH stimulation. However, in 4 cases out of 18, inhibition seemed to be slight, basal values remained between 210 and 330 μU/ml, and in 2 of these cases, increase after TRH was higher than 800 μU/ml.

Effect on other hormonal secretions (table 3).

Hormonal secretions varied from one subject to another. The average showed an increase of basal FSH and LH values, but the variations were non-significant. Urinary FSH was slightly lower, whereas urinary LH increased (P = 0.05). The surge of LH and FSH after LH-RH stimulation was unchanged. Plasma testosterone and urinary androgens (A + E) were lower, but only urinary androgen decrease was significant (P = 0.05), this decrease being essentially related to the etiocholanolone.

A separate study of the two patient groups (PO > 300 μU/ml on the one hand, PO < 300 μU/ml and ΔP > 800 μU/ml on the other) showed comparable results. The absence of a significant difference seemed to be due to the small number of patients (9) in each group.

Spermogram study.

In the whole group (18 subjects) the treatment caused large changes in the number of spermatozoa per ml ; this significantly increased from $15.5 \pm 2.8 \times 10^6$ before treatment (extreme values 0.35 to 45.0×10^6) to $31.6 \pm 6.1 \times 10^6$ after treatment (extreme values 0.35 to 105.0×10^6). On the other hand, motility one hour after emission, the number of normal forms and the volume of ejaculation were not statistically

modified. Thus, 11 subjects showed definite improvement, 3 remained unchanged, 2 presented more spermatozoa per ml but a considerable decrease in motility, and 2 showed a decrease in the number and the motility of spermatozoa.

TABLE 3

Evolution of hormonal secretion and spermograms before and after treatment with bromocriptine in infertile men (mean ± SEM)

	Groups Number	Total subjects 18		Basal PRL > 300 μU/ml 9		Basal PRL < 300 μU/ml ΔP > 800 μU/ml 9	
	Treatment	before	after	before	after	before	after
plasma hormones	basal FSH mUI/ml	7.2 ± 1.2	8.3 ± 1.7	5.0 ± 0.9	7.8 ± 2.5	11.6 ± 1.9	9.9 ± 2.5
	FM mUI/ml	17.0 ± 2.3	16.0 ± 2.8	12.7 ± 2.3	13.9 ± 3.9	25.5 ± 3.3	21.1 ± 4.5
	basal LH mUI/ml	5.8 ± 0.6	7.0 ± 0.8	6.2 ± 1.0	6.4 ± 1.1	5.2 ± 0.6	7.9 ± 1.3
	LM mUI/ml	25.0 ± 2.6	23.0 ± 3.0	20.4 ± 3.0	21.3 ± 4.6	32.4 ± 3.7	23.7 ± 2.8
	Testosterone ng/ml	7.9 ± 0.7	5.7 ± 1.0	7.9 ± 0.8	6.2 ± 1.9	7.5 ± 1.7	4.9 ± 0.4
urinary steroids	Androsterone (A) mg/24 h	3.9 ± 0.4	3.1 ± 0.5	3.8 ± 0.4	3.4 ± 0.6	4.5 ± 0.7	2.8 ± 0.3
	Etiocholanolone (E) mg/24 h	2.7 ± 0.4	1.7 ± 0.2 *	3.1 ± 0.4	1.9 ± 0.2 *	2.0 ± 0.2	1.2 ± 0.3
	A + E mg/24 h	6.6 ± 0.6	4.9 ± 0.6 *	7.0 ± 0.7	5.3 ± 0.8	6.6 ± 0.8	4.0 ± 0.5
spermograms	Volume (ml)	2.9 ± 0.4	3.0 ± 0.4	2.8 ± 0.6	3.3 ± 0.5	3.0 ± 0.5	2.9 ± 0.6
	Number (10^6/ml) of spermatozoa	15.5 ± 2.8	31.6 ± 6.0 *	17.3 ± 3.3	44.7 ± 10.3 *	13.9 ± 4.8	20.2 ± 5.6
	Motility p. 100	50 ± 3	45 ± 4	51 ± 4	53 ± 3	47 ± 4	34 ± 7
	Normal forms p. 100	74 ± 3	69 ± 3	76 ± 3	74 ± 5	72 ± 4	64 ± 5

* : Statistically different than the corresponding value before treatment, p < 0,05.
ΔP : Increase of prolactinemia after 200 μg IV of TRH.
FM, LM : Peak of FSH and LH after 50 μg IV of LHRH.

In the 9 subjects who presented basal prolactinemia higher than 300 μU/ml before treatment, we noted a significant increase in the number of spermatozoa per ml, i.e. $17.0 ± 3.3 \times 10^6$ before treatment to $44.7 ± 10.3 \times 10^6$ after treatment (extreme
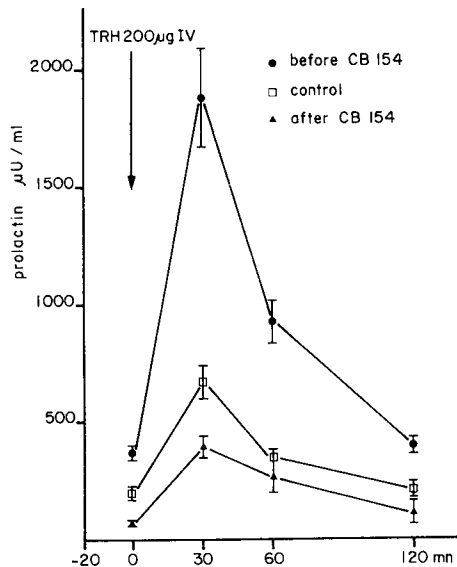
FIG. 1. — Prolactin secretion (basal level and response after TRH)
before and after treatment with bromocriptine in infertile men (mean ± SEM).

value were from 0.4 to 36.0 × 10⁶/ml and from 1.4 to 105.0 × 10⁶/ml, respectively).
Eight subjects showed definite improvement, the increase being higher than 60 p. 100
for each individual. In one case, the number of spermatozoa was only slightly modified.

In the 9 subjects who presented basal prolactinemia lower than 300 μU/ml before
treatment and increased prolactineamia higher than 800 μU/ml after TRH (ΔP),
we noted in 3 cases a definite increase in the number of spermatozoa, in 2 cases
no change, in 2 cases more spermatozoa per ml but a noticeable decrease in moti-
lity, and in 2 cases a considerable decrease in both number and motility. A statis-
tical study of the spermograms of the whole group did not reveal any significant
variations.

Discussion.

The functioning and degree of malfunction of the hypothalamopituitary-gonadic
axis in infertile men can be defined using the LH-RH test (Franchimont et al., 1973 ;
Boucher et al., 1976). Basal FSH level and cumulative responses after LH-RH increased
when spermatogenesis was blocked, whereas LH secretion was normal or increased
slightly. This result would suggest the germinal cell secretion of an « inhibin » and
its preferential intervention in FSH feedback (Setchell, 1974 ; Franchimont et al.,
1975).

Prolactin and gonadotropins.

The prolactin level we observed before or after TRH in a normal healthy man
corresponds to that noted by other authors (L'Hermite et al., 1975 ; Franchimont et al.,

1976). Among the sterile men, about 40 p. 100 presented increased prolactin secretion before or after TRH ; this was most frequent in the case of exaggerated LH and/or FSH responses after LH-RH stimulation ; it was also seen in about 30 p. 100 of the infertile normogonadotropics. In most of the groups, there is a correlation between prolactin and gonadotropin which agrees with the results noted after TRH by Mortimer et al. (1973a) and the observations on patients presenting hyperprolactinemia and hypogonadism (Mortimer et al., 1973b). It therefore seems that in man the secretion of the hormones FSH, LH and prolactin generally evolves in the same way, and not inversely, as some observations on animals would lead us to believe (Ben-David, Danon and Sulman, 1971). Hyperprolactinemia is frequently related to LH deficiency in humans (Boyar et al., 1974) and this must be associated to hypothalamo-pituitary tumoral processes.

Prolactin and gonadic function.

The role of prolactin on the gonadic function is still not well known, although much discussed.

a) *Some studies favour a stimulating effect of prolactin on LH and androgens. In vitro* prolactin potentializes LH action on testis synthesis and secretion of testosterone (Hafiez, Bartke and Lloyd, 1972) ; it stimulates the prostate gland in man (Farnsworth, 1972) as well as in rat (Kledzik et al., 1976) ; it activates prostate gland protein and RNA synthesis, but does not modify the testosterone metabolism at that level (Johansson, 1975, 1976).

Prolactin associate with LH *in vivo* restores normal testosteronemia in hypophysectomized rat (Hafiez, Llyod and Bartke, 1972), and intervenes in testis and accessory organ development (Negro-Vilar, Krulich and MacCann, 1973). In the male hamster exposed to short day length, prolactin significantly increases the weight of testis, seminal vesicles and prostate gland, as well as increasing plasma testosterone level (Bartke, Croft and Dalterio, 1975). Testosterone peaks in man are preceded by peaks of LH and prolactin 60 min beforehand (Rubin, Poland and Tower, 1976), and an increase in prolactin is followed by an increase in testosterone (Rubin et al., 1975). For Ambrosi et al. (1976), hyperprolactinemia induced by sulpiride is accompanied by increased response to testosterone after HCG stimulation.

b) *On the other hand, some data indicate prolactin inhibitory activity.* Experimental hyperprolactinemia in women is accompanied by a shorter luteal phase during which LH, FSH and progesterone values are significantly lower (Delvoye et al., 1974). TRH treatment producing hyperprolactinemia is followed by suppression of the preovulatory LH surge (Bohnet, Dahlen and Schneider, 1974). Hyperprolactinemia in women is very often accompanied by amenorrhea, and in men by impotence or hypogonadism (Thorner et al., 1974 ; Fossati, Strauch and Tourniaire, 1976) ; androgen secretion consecutive to HCG treatment is greater when prolactin is inhibited (Besser and Thorner, 1975).

In rat, experimental hyperprolactinemia, consecutive to transplant of a prolactin pituitary tumor, is followed by a lower testosterone level, genital atrophy and spermiogenetic arrest (Fang, Refetoff and Rosenfield, 1974). The high prolactin levels may

contribute to long-term inhibition of the estrous cycle in female rat (Kerdelhué et al., 1976).

Our results would suggest double prolactin action ; the correlations between prolactin and plasma or urine androgens seem to indicate that prolactin, alone or in association with gonadotropins, stimulates the secretion and metabolism of androgens. On the other hand, negative prolactin-testosterone correlation in the cases of very early spermatogenetic arrest would suggest inhibitory action. We think the prolactin effect in man depends on the secretion level of that hormone and on gonadotropin balance, i.e. prolactin appears to stimulate the androgenic function in nearly normal conditions, but on the contrary, to inhibit it when there is hypersecretion of prolactin and FSH or LH.

Bromocriptine treatment.

Most of the studies using bromocriptine have been carried out on women, in particular during the amenorrhea-galactorrhea syndrome. This rye ergot alkaloid inhibits the secretion of prolactin (Del Pozo et al., 1972), and its use in cases of hyperprolactinemia provokes the reappearance of the menstrual cycle in most cases (Besser et al., 1972 ; Del Pozo et al., 1974 ; Seki, Seki and Okumura, 1975 ; Fossati, Strauch and Tourniaire, 1976). Bromocriptine does not modify LH or FSH, but increases estradiol secretion (Seppala et al., 1976). For Del Pozo et al. (1974) bromocriptine treatment is usually accompanied by an increase of LH and FSH.

The treatment of men with bromocriptine seems to have a variable action on LH, FSH and androgens. On an average, it appears to increase FSH and LH, and decrease testosterone and urinary androgens. The most interesting data show a large increase in the number of spermatozoa that appears after hyperprolactinemia has been inhibited for one month. These results concord with those of other authors studying the improvement of fertility in men (Besser and Thorner, 1975) ; they are in contradiction with the data on prolactin-spermatogenetic relationships in animals such as the studies of Woods and Simpson (1961) on hypophysectomized rat, Bartke (1971) on hypophysectomized mouse and Bartke and Llyod (1970) on dwarf mouse which have effectively demonstrated the synergic action of prolactin and of LH in maintaining or restoring spermatogenesis. This action seems to be secondary to increased biosynthesis and testosterone secretion (Hafiez, Lloyd and Bartke, 1972).

Therefore, hyperprolactinemia in man would seem to slow down spermatogenesis ; in animals, the absence of prolactin is prejudicial to spermatogenesis, but prolonged hyperprolactinemia may cause blockage of spermatogenesis (Fang, Refetoff and Rosenfield, 1974). Thus, there may be double prolactin action, favorable with normal or low levels, and unfavorable with high levels.

Knowing that, as in other mammals, the length of the various spermatogenetic stages in man is independent of endocrine conditions (Heller and Clermont 1963, 1964), the impact of hyperprolactinemia may thus be determined. We observe improvement 25 to 30 days after the beginning of the treatment. Since 24 hours are required to transform spermatocytes II into spermatids, spermiogenesis (spermatids-spermatozoa) lasts about 23 days, and it takes at least one day for spermatozoa to pass into the epididymis (Heller, Teshima and Rowley, 1969) the inhibitory effect of hyperprolactinemia

is probably situated at the spermatocyte II or the spermatid stage, or at the time of epididymal transit.

Conclusion.

In most cases, the degree of hypothalamo-pituitary-gonadic axis malfunction may be determined by the LH-RH test. FSH, in particular, increases progressively as spermatogenetic blockage occurs at earlier stages, thus confirming germinal cell secretion of an inhibin exerting negative feedback on FSH secretion.

In the absence of any discernible tumoral process, the study of prolactin secretion shows that 40 p. 100 of sterile men present a high level of prolactinemia before or after stimulation by TRH. Prolactin, FSH and LH usually evolve in the same way ; it would therefore seem that there is no antagonism between prolactin and gonadotropin secretion in man. The correlation between prolactin and androgens indicates prolactin stimulation of the secretion and the metabolism of androgens. However, since this correlation disappears in some groups, and may even become negative, an inhibition may appear, particularly in cases of hyperprolactinemia. This may be due to gonadotropin inhibition of peripheral receptors.

Prolactin secretion greatly diminishes when men presenting a high level are treated with bromocriptine. Changes in LH, FSH and androgens vary from one subject to another ; the average result is increased FSH and LH while androgens decrease. The large augmentation in the number of spermatozoa per ml after a one-month treatment would suggest that hyperprolactinemia inhibits the final stages of spermatogenesis (spermatocytes II or spermatids) and/or epididymal transit. Bromocriptine may represent an efficient therapy for masculine infertility in cases where hyperprolactinemia is present. Further studies are necessary in order to confirm these first results, and to determine the consequences of this treatment on a long-term basis.

8ᵉ Colloque de Neuroendocrinologie. — Table ronde Prolactine.
Tours, 7 septembre 1976.

Résumé.   L'objet du présent travail est d'étudier la sécrétion de prolactine chez l'homme stérile et l'influence d'un traitement par la bromoergocryptine.

Douze hommes témoins et quatre-vingt-dix hommes stériles sont soumis à un bilan complet : spermogrammes, dosages radioimmunologiques de FSH, LH prolactine et testostérone plasmatiques ; dosage par chromatographie en phase gazeuse des androgènes urinaires ; tests de stimulation par le LHRH et le TRH. 18 patients stériles présentant une sécrétion élevée de prolactine sont traités pendant 1 mois par la bromoergocryptine (5 mg par jour) et subissent un nouveau bilan identique.

1. *Les spermogrammes et le test au LHRH permettent* d'individualiser cinq groupes :

(1) témoins ; (2) oligospermiques eugonadotropes ; (3) oligospermiques hypogonadotropes ; (4) oligospermiques hypergonadotropes : fortes réponses en LH et parfois FSH,

après LHRH ; (5) azoospermiques ou oligospermiques sévères avec blocage plus ou moins précoce de la spermatogenèse.

2. *L'étude de la sécrétion de prolactine* et de ses corrélations avec FSH, LH, testostérone et androgènes urinaires montre que :

— environ 40 p. 100 des hommes stériles ont une sécrétion de prolactine supérieure à la normale (avant ou après TRH) ;
— la prolactine, FSH et LH évoluent le plus souvent dans le même sens ;
— la prolactine est corrélée aux androgènes sanguins et urinaires dans la plupart des groupes. Cette corrélation devient négative dans les cas de blocage précoce de la spermatogenèse.

3. *Le traitement par la bromoergocryptine* pendant 1 mois a pour conséquences :

— une diminution de la prolactinémie et de la libération de prolactine au cours d'une stimulation par le TRH ;
— en moyenne une augmentation de FSH et de LH et une diminution des androgènes. Ces modifications sont peu importantes et très variables d'un sujet à l'autre ;
— une augmentation significative du nombre de spermatozoïdes qui passe de 15.10^6/ml à 31.10^6/ml.

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