EFFECT OF CLOMIPHENE ON FERTILITY IN MALE RATS

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Summary. The effects of long-term administration of clomiphene on immature, intact male rats and their reproductive performance following cessation of treatment are reported. Clomiphene, at a dose of 250 $\mu\text{g/day}$ or higher, inhibited spermatogenesis at the primary spermatocyte stage, the Leydig cells were atrophic and consequently the accessory glands were non-secretory. The testis resumed normal spermatogenesis immediately following withdrawal of treatment and spermatozoa appeared in the seminiferous tubules within 30 days of the period of recovery. The recovered males sired normal young when caged with virgin cycling females. It is suggested that the inhibitory effects on the testes and accessory glands following long-term administration of clomiphene are due to the oestrogenicity of the compound which may modify the synthesis and/or release of the gonadotrophins mediated through the hypothalamo-hypophyseal axis.

The results are discussed in relation to the sequence of recovery of the gonads and accessory glands.

INTRODUCTION

Considerable attention has been paid in recent years to the study of non-steroidal compounds which inhibit gonadal activity and other associated endocrine functions (Fridhandler & Pincus, 1964; Lerner, 1964; Kincl, Maqueo & Dorfman, 1965; Nelson, 1965). Clomiphene, 1-[-*p*(β -diethyl-aminoethoxy)-phenyl]-1,2, diphenyl-2-chloroethylene, a non-steroidal triphenyl derivative of chlorotrianisene, has varied biological effects in animals and man. It is known to inhibit endogenous gonadotrophic activity and to reduce fertility in rats and rabbits (Holtkamp, Greslin, Root & Lerner, 1960; Barnes & Meyer, 1962; Chang, 1964; Prasad, Kalra & Segal, 1965; Davidson, Wada & Segal, 1965; Prasad & Kalra, 1967). Brief reports on the effects of clomiphene on the reproductive physiology of male rats (Holtkamp *et al.*, 1960; Nelson & Patanelli, 1962; Roy, Mahesh & Greenblatt, 1964; Nelson, 1965) show that clomiphene inhibits testicular function. On the other hand, Heller & Moore (1963), Jungck, Roy, Greenblatt & Mahesh (1964) and Mellinger & Thompson (1966) reported an increase in sperm count in oligospermic men following clomiphene treatment.

This study describes the effects of long-term administration of clomiphene on immature, intact male rats and their reproductive performance after recovery from treatment. Similar studies on female rats are reported elsewhere.

MATERIAL AND METHODS

Immature colony-bred rats originally derived from the Wistar strain were used in these experiments. Rats were maintained in an air-conditioned room ($78 \pm 2^\circ \text{F}$), and fed a standard diet. Water was always available.

Treatment with clomiphene was initiated on Day 22 immediately after weaning. Clomiphene was fed by oral gavage in 0.25 ml of olive oil once daily, six times a week, for a total period of 25 or 55 days. Control groups were fed a similar amount of the vehicle, olive oil. One group of rats was autopsied on Day 22 and served as initial control, while the other groups were autopsied 24 hr after the last administration of the drug or oil. The testes, prostate, seminal vesicles, thyroid and adrenals were quickly removed and weighed on a precision torsion balance and fixed in Bouin's fixative for histological studies. Sections of the testis and accessory glands were cut at 6μ and stained with PAS-Haematoxylin or Haematoxylin-Eosin. The pituitary glands were weighed and fixed in Dawson's fixative; sections cut at 6μ were stained in PAS-Orange G.

Recovery studies

Rats fed 250 $\mu\text{g/day}$ of clomiphene, six times a week for 55 days, beginning from Day 22 were used in these studies. Groups of six rats each were autopsied at intervals of 10 days following the cessation of treatment. Different stages of the seminiferous epithelium were identified following the scheme of Leblond & Clermont (1952). One group of rats which was allowed to recover for 36 days was caged with virgin cycling females to study the fertility of males after recovery. Vaginal smears were taken daily throughout the 90-day period when males and females remained together. Number of litters born and litter size were recorded. Untreated males and females of approximately the same age were caged together for a similar period and served as controls.

The similarity of the antigonadotrophic activity of clomiphene and of oestrogen was investigated by injecting subcutaneously two groups of rats with 5 $\mu\text{g/day}$ of oestradiol benzoate in 0.25 ml of olive oil for 25 and 55 days respectively, beginning on Day 22. Rats were autopsied on the day following the last treatment and the tissues were processed as described earlier.

All the rats were weighed once every week until autopsy.

RESULTS

With increase in the dose of clomiphene, there is a graded decrease in growth rate. The growth rate of oestrogen-treated animals is similar to that of animals receiving 1 mg/day of clomiphene. Rats which were treated with the smallest dose of clomiphene (34 $\mu\text{g/day}$) did not show any reduction in body weight and resembled the controls (Table 2).

Low dose series

The results of various treatments on testes and accessory glands are summarized in Tables 1 and 2. Rats treated with 34 $\mu\text{g}/\text{day}$ for 55 days did not show any retardation of growth (Table 2). Their testes were well developed and descended into scrotal sacs. Spermatogenesis was normal. However, the accessory glands were reduced in weight as well as in secretory activity. With increase in the dose of clomiphene to 125 $\mu\text{g}/\text{day}$, the testes were reduced in weight to 694 ± 98 mg compared to 1976 ± 139 mg in the control group (Table 2). The development of the scrotum was slightly retarded. Spermatogenesis was arrested in the early spermatid stage (step 7). The Leydig cells were atrophic; consequently, all the accessory glands showed a further reduction in weight and in secretory activity.

TABLE 1

EFFECT OF CLOMIPHENE ON TESTES AND ACCESSORY GLANDS: SHORT-TERM TREATMENT

Treatment†	Body weight (g)	Testes (mg)	Ventral prostate (mg)	Seminal vesicle (mg)	Adrenal (mg)	Thyroid (mg)	Pituitary (mg)
Initial control (Day 22) (8)	27	163 ± 8	6.0 ± 0.6	7.0 ± 0.6	13.0 ± 1.0	5.0 ± 0.04	1.9 ± 0.3
Control, no treatment (6)	82	880 ± 122	22.5 ± 4.0	19.3 ± 1.3	23.5 ± 1.3	11.7 ± 0.9	3.1 ± 0.7
Clomiphene 250 $\mu\text{g}/\text{day}$ (6)	64	$135 \pm 5^{**}$	$4.7 \pm 0.3^{**}$	$10.0 \pm 0.3^{**}$	26.0 ± 0.9	11.0 ± 0.5	3.3 ± 0.1
Oestradiol 5 $\mu\text{g}/\text{day}$ (4)	62	141 ± 6	$8.0 \pm 1.1^*$	$30.2 \pm 2.4^*$	25.7 ± 1.0	12.3 ± 2.8	3.3 ± 0.7

Figures in parentheses indicate the number of animals.

* $P < 0.05$.** $P < 0.001$.

† Treatment (6 times a week) initiated on Day 22 and continued for 25 days. Autopsy on Day 48.

High dose series

Rats treated with 250 $\mu\text{g}/\text{day}$ of clomiphene for 25 or 55 days showed a marked inhibition of testicular activity. The scrotal sacs were not developed; the testes remained either abdominal or inguinal in position and could not be palpated (Pl. 1, Fig. 1). The mean testes weight was reduced from 1976 ± 139 mg in the controls to 326 ± 56 mg (Table 2); spermatogenesis was arrested at the primary spermatocyte stage (Pl. 2, Fig. 3). Mitoses in the spermatogonia were apparently normal and uninhibited, similar to that seen in initial controls (Pl. 2, Figs. 6 and 7). Successive waves of primary spermatocytes formed by continued spermatogonial divisions were apparently desquamated into the lumen of the seminiferous tubules and could be seen in the epididymis also. The Sertoli cells in the controls were orientated with their long axes parallel with or at right angles to the membrana propria (Pl. 3, Fig. 13), while in the clomiphene-treated rats, the Sertoli cells retained their orientation and appearance as in the 22-day-old immature rats (Pl. 2, Figs. 3 and 7; and 2 and 6). They were arranged in the form of a second layer next to the spermatogonia and were devoid of cytoplasmic granules. Leydig cells were sparse in number

TABLE 2
EFFECT OF CLOMIPHENE ON TESTES AND ACCESSORY GLANDS: LONG-TERM TREATMENT

Treatment†	Body weight (g)	Testes (mg)	Ventral prostate (mg)	Seminal vesicle (mg)	Adrenal (mg)	Thyroid (mg)	Pituitary (mg)
Control (no treatment)	(8) 139	2016 ± 101	154 ± 6.9	178 ± 11	30 ± 2.2	21 ± 1.5	5.4 ± 0.28
Control (Olive oil)	(8) 122	1976 ± 139	157 ± 26	192 ± 29	32 ± 2.2	16.7 ± 0.6	4.3 ± 0.16
Clomiphene 34 µg/day	(7) 130	1545 ± 180	44 ± 15*	69 ± 12.9*	31 ± 2.0	18.5 ± 3.2	4.3 ± 0.27
Clomiphene 125 µg/day	(8) 105	694 ± 98**	14 ± 3.9**	27 ± 6.1**	27 ± 1.7	13.7 ± 1.4	2.7 ± 0.2**
Clomiphene 250 µg/day	(12) 112	326 ± 56**	11 ± 0.9**	17 ± 2.2**	32 ± 1.7	15.8 ± 1.2	3.2 ± 0.19**
Clomiphene 1 mg/day	(5) 87	214 ± 32**	15.4 ± 1.1**	17 ± 2.4**	30 ± 1.1	10.4 ± 0.9**	3.8 ± 0.2
Oestradiol 5 µg/day	(6) 95	163 ± 22**	13.8 ± 12.5**	38.6 ± 2.8**	34 ± 1.4	12.8 ± 1.0*	4.0 ± 0.3

Figures in parentheses indicate the number of animals.

* $P < 0.05$.

** $P < 0.001$.

† Treatment (6 days a week) initiated on Day 22 and continued for 55 days. Autopsy on Day 78.

and showed atrophy. The seminal vesicles and the prostate were markedly reduced in weight and were non-secretory. In the prostate epithelial cell, the supranuclear zone corresponding to the Golgi elements was absent while in the controls this region was well developed and conspicuous.

Similar changes in the testis and accessory glands were seen in rats treated with 1 mg/day of clomiphene or 5 µg/day of oestradiol benzoate for 55 days. Spermatogenesis was arrested in the primary spermatocyte stage in the oestradiol-treated rats as in the clomiphene-fed groups, but in a few tubules early spermatids were also observed (Pl. 2, Figs. 4 and 8; 5 and 9). Oestradiol caused a marked shrinkage of the seminiferous tubules and thinning of the tunica propria. The accessory reproductive organs were non-secretory. However, the weights of the seminal vesicles in the oestradiol-treated group were nearly double that of the clomiphene-fed group, due primarily to fibromuscular

TABLE 3
RECOVERY OF THE TESTES AND ACCESSORY GLANDS FOLLOWING CESSATION OF
CLOMIPHENE TREATMENT†

Recovery period (days)	Body weight (g)	Testes (mg)	Ventral prostate (mg)	Seminal vesicle (mg)	Adrenal (mg)	Thyroid (mg)	Pituitary (mg)
No recovery (5)†	112	356 ± 106	10.5 ± 1.4	18.6 ± 3.7	33 ± 2.6	19 ± 1.9	3.4 ± 0.15
10 (6)	110	725 ± 63	20.3 ± 5.1	33.3 ± 4.9	30 ± 1.4	13.6 ± 1.2	3.0 ± 0.13
20 (6)	122	1284 ± 97	56 ± 10.0	103 ± 27.0	31 ± 2.6	18.6 ± 0.9	3.6 ± 0.3
30 (6)*	131	1436 ± 148	71 ± 15.0	134 ± 55.0	31 ± 2.5	14 ± 0.26	4.3 ± 0.4
Control (5)*	141	2106 ± 163	124 ± 15.0	248 ± 19.0	38 ± 3.9	14 ± 1.3	5.0 ± 0.1
Percentage recovery on Day 108 compared with control	—	67	57	54	—	—	86

Figures in parentheses indicate the number of animals.

*108-day-old rats.

†78-day-old rats.

‡Rats were treated with 250 µg/day of clomiphene (6 times a week) for 55 days beginning on Day 22.

hypertrophy (Table 2). There was no fibromuscular hypertrophy of the seminal vesicles of rats treated with 1 mg/day of clomiphene.

In all the clomiphene-fed groups, the weights of the thyroid and adrenal glands did not differ significantly from those of the olive oil or untreated controls (Tables 1 and 2). However, rats treated with oestrogen and the highest dose of clomiphene (1 mg/day) showed a marked reduction in the weight of the thyroid (Table 2). The pituitaries of the 125 and 250 µg/day clomiphene-fed groups were significantly reduced in weight while the weights of the pituitaries of the other treated groups did not differ from those of the controls (Tables 1 and 2).

Recovery

Table 3 shows the extent of recovery of the weights of the testes and accessory glands following the cessation of clomiphene treatment. Rats which were treated with 250 µg/day of clomiphene for 55 days were killed in groups of six at intervals of 10 days following the last treatment. At the end of 30 days of

recovery the testes attained the weight of 1436 ± 148 mg compared to that of controls (2106 ± 163 mg) indicating a recovery to the extent of 67% from the basal level of 356 ± 106 mg at the end of the treatment on Day 78. The weights of the prostate and seminal vesicles recovered to 57% and 54% of those of the controls respectively. Pituitary weights did not show any variation while the thyroid showed marked fluctuation in weight without any relation to the sequence of recovery of the gonads and accessory glands. The testis showed marked ability to resume normal spermatogenesis immediately following withdrawal of treatment. Spermatogenesis which was arrested at the primary spermatocyte stage during clomiphene administration advanced to the cap-phase of spermiogenesis (step 7) within 10 days of cessation of treatment (Pl. 3, Fig. 10); the Leydig cells appeared to be still atrophic. Young spermatids (stage XIV, step 14) were noticed in a large number of tubules 20 days after the termination of treatment (Pl. 3, Fig. 11) and the accessory glands showed signs of secretory activity. Within 30 days of the recovery period, spermatogenesis was nearly normal with a large number of tubules full of spermatozoa released into the lumen (Pl. 3, Fig. 12). Spermatogenesis in the controls was normal (Pl. 3, Fig. 13). Four female rats of proved fertility, which were caged with the recovered male rats, showed six matings during the 90 day period. One rat mated five times but did not show any signs of pregnancy while the other three females had five litters during the same period, with an average litter-size of five (Kalra & Prasad, 1967).

DISCUSSION

A variety of steroidal and non-steroidal drugs inhibit spermatogenic activity (Holtkamp *et al.*, 1960; Albert, 1961; Gaunt, Chart & Ronzi, 1963; Fridhandler & Pincus, 1964; Kincl *et al.*, 1965). Our results are essentially in agreement with those of Nelson & Patanelli (1962). They reported the arrest of spermatogenesis at the spermatid stage in rats treated with varying doses of clomiphene beginning on Day 30, while in our studies spermatogenesis was arrested in the primary spermatocyte stage in rats in which treatment was initiated on Day 22. This difference is probably due to the age at initiation of treatment and the terminal stage in spermatogenesis present at that time. The time of initiation of treatment appears to be critical in the inhibition of spermatogenesis (Leatham, 1942).

The antispermatogenic activity of clomiphene may be due: (a) to inhibition of synthesis and/or release of gonadotrophins from the pituitary, (b) to a direct inhibitory effect on the testis and accessory reproductive organs, and (c) to the inhibition of circulating gonadotrophins. Holtkamp *et al.* (1960) and Nelson & Patanelli (1962) assayed the pituitaries of clomiphene-treated rats and showed a marked reduction in gonadotrophin content of pituitaries. Roy *et al.* (1964) reported that low doses of clomiphene (0.1 to 0.5 mg/kg/day for 34 days) increased the weights of the ventral prostate while higher doses inhibited the increase in weight of the accessory glands. They interpreted these results to mean that, at low dose levels, clomiphene facilitates and/or enhances the release of ICSH from the pituitary while at higher dose levels pituitary gonadotrophins

are inhibited. Our studies on the cytology of the pituitary glands of male rats treated with 125 and 250 μg of clomiphene per day show that the gonadotrophs are degranulated (Pl. 4, Fig. 15). With increase in the dose of clomiphene to 1 mg/day, the gonadotrophs are completely degranulated and are indistinguishable from the chromophobes; there is an apparent increase in the number of orangeophilic acidophils (Pl. 4, Fig. 16). A similar picture is seen in the pituitaries of rats treated with 5 μg of oestradiol per day (Pl. 4, Fig. 17). In another study (Kalra & Prasad, 1967) adult female rats were treated daily with 0.5 and 1 mg of clomiphene for 32 days beginning 2 months after spaying; another group was injected with 1 μg of oestradiol per day for a similar period. The gonadotrophs were degranulated to the same extent in both the clomiphene- and oestrogen-treated groups. Assays of the pituitaries showed a marked decrease in the gonadotrophin content parallel with degranulation of the gonadotrophs. These studies indicate that arrest of spermatogenesis in clomiphene-fed rats may be due to inhibition of synthesis and/or release of gonadotrophins from the pituitary.

The recovery of the testes and accessory glands to a stage of normal sperm production within 30 days after the cessation of clomiphene treatment suggests that clomiphene does not have a direct inhibitory effect on the testis.

The possibility of inhibition of circulating gonadotrophins is not likely since Holtkamp *et al.* (1960), Roy *et al.* (1964) and France & Pincus (1964) showed that clomiphene does not inhibit exogenously administered gonadotrophins.

Clomiphene (MRL-41), formerly called chloramiphene, is a close analogue of the synthetic oestrogen chlorotrianisene (TACE) and ethamoxxytriphetol (MER-25). These compounds have a variable degree of oestrogenic and anti-oestrogenic properties. Clomiphene is more oestrogenic than MER-25 (Lerner, 1964; Emmens, 1965) and this apparently accounts for its greater antigonadotrophic activity. Our observations on the effect of clomiphene on the pituitaries of ovariectomized rats, cited earlier, indicate that the effects of clomiphene are similar to those of oestrogen. Degranulation of gonadotrophs, decrease in gonadotrophin content, hypertrophy and hyperplasia of acidophils are well known effects of oestrogens (Greep & Jones, 1950; Purves, 1961).

The general conclusion which can be drawn from this discussion and a perusal of the literature is that clomiphene and related compounds may act as oestrogens on some tissues and as anti-oestrogens on other target sites depending upon the threshold for the different target organs. Our studies indicate that at the dose level of 250 μg and 1 mg/day, clomiphene inhibited the development of the testis and accessory glands but the same dose did not produce fibromuscular hypertrophy of the seminal vesicle. On the other hand, 5 μg of oestrogen caused a marked fibromuscular hypertrophy of the seminal vesicles. Lerner (1964) observed that MER-25 selectively inhibited scrotal development, without in any way affecting the development and activity of the testis, indicating a differential target organ response to the weak oestrogenicity of the compound. At the dose levels we have used, clomiphene inhibits both scrotal and gonadal development, possibly indicating the higher oestrogenicity of the compound.

The testis and accessory glands of reproduction recover from the inhibitory effects of clomiphene within 30 days following withdrawal of treatment.

The weights of the testes increased gradually following cessation of treatment and returned to 67% of those of the controls at the end of 30 days; at the same time the accessory glands showed a lag in recovery as evidenced by the weights of seminal vesicle and ventral prostate which recovered to 54% and 57% of those of the control values respectively. It is interesting to note that the accessory reproductive organs recover earlier than the testes in rats treated with stilboestrol (Snair, Jaffray, Grice & Pugsley, 1954).

Recently Kar, Chowdhury, Chowdhury, Kamboj & Chandra (1965) reported marked reduction in testis weights in monkeys treated chronically with oestrogen. The inhibition of testicular activity at the spermatogonial stage in monkeys differs from the inhibition of spermatogenesis at the primary spermatocyte stage in rats treated with clomiphene, which is weakly oestrogenic. The weights of seminal vesicles and prostates of monkeys treated with oestrogen did not differ markedly from those of controls, but fructose and zinc levels in the seminal vesicle and prostate, respectively, were significantly lowered. The maintenance of the weight of the accessory glands of reproduction during oestrogen treatment may be due to a direct stimulatory action of oestrogen on the fibromuscular tissue (Price & Williams-Ashman, 1961). Rats treated with clomiphene did not show any increase in the weights of accessory glands, possibly indicating the low oestrogenicity of the compound at the dose levels used.

In monkeys treated with oestrogen, the testes showed recovery to the secondary spermatocyte stage at the end of the 60-day recovery period, while, in rats, spermatogenesis was completely restored within 30 days following withdrawal of treatment. This lag in the recovery of the testis in monkeys may be due to the long time needed for the completion of spermatogenesis. In monkeys, accessory glands regain their normal functional status within 60 days following withdrawal of oestrogen treatment but spermatogenic activity in the testis is not then fully restored. Kar *et al.* (1965) interpreted these results to mean: (a) that either oestrogen promoted a preferential synthesis of ICSH by the pituitary for a substantial part of the post-treatment period, as revealed by the recovery of accessory reproductive organs, and FSH was probably elaborated in small amounts insufficient to restore spermatogenesis, or (b) that oestrogen treatment, by a direct action on the testis, had rendered it insensitive to FSH. These suggestions remain to be tested in rats.

It is possible, therefore, that the observed inhibitory effects on the testes and accessory glands, following long-term administration of clomiphene, are due to the oestrogenicity of the compound modifying the synthesis and/or release of gonadotrophins, mediated through the hypothalamo-hypophysial axis. Complete recovery of spermatogenesis following withdrawal of clomiphene treatment indicates that the effects of the treatment are transient on the hypophysial-gonad system.

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EXPLANATION OF PLATES

PLATE 1

FIG. 1. (A) External appearance of rats treated with 250 μg of clomiphene per day (left), olive oil (centre) and 5 μg of oestradiol per day (right) for 55 days, beginning on Day 22. The scrotal sac is not developed in the clomiphene- and oestrogen-treated animals. (B) Gross appearance of testes obtained from olive oil-treated (a) and clomiphene-treated rats (b) as described in (A).

PLATE 2

FIG. 2. Transverse section of the testis of a 22-day-old rat (initial control). Spermatogenesis has advanced to the primary spermatocyte stage. Note the Sertoli cells forming a layer over the spermatogonia. $\times 350$.

FIG. 3. Transverse section of the testis of a 78-day-old rat treated with 250 μg of clomiphene per day. Spermatogenesis is arrested at the primary spermatocyte stage; spermatocytes which are desquamated are seen in the lumen of the seminiferous tubule. Sertoli cells are arranged as in Fig. 2. Interstitial cells are non-secretory. $\times 350$.

FIG. 4. Transverse section of the testis of a 78-day-old rat treated with 1 mg of clomiphene per day. The effect of the drug on spermatogenesis is the same as that in Fig. 3. $\times 350$.

FIG. 5. Transverse section of the testis of a 78-day-old rat treated with 5 μg of oestradiol per day. The histology of the testis is the same as that in Figs. 3 and 4. Note the thin and wrinkled membrana propria. $\times 350$.

Figs. 6, 7, 8 and 9 are higher magnifications of testes corresponding to those in Figs. 2, 3, 4 and 5. Spermatogonial mitoses are not affected by the treatments and are apparently normal. $\times 840$.

PLATE 3

Figs. 10, 11, 12. Recovery of spermatogenic activity following withdrawal of clomiphene treatment (250 $\mu\text{g}/\text{day}$ for 55 days beginning on Day 22). $\times 1000$.

FIG. 10. Recovery of spermatogenic activity 10 days after cessation of treatment. Tubules show advance of spermatogenesis up to the cap-phase (Steps 1–7).

FIG. 11. Advance of spermatogenesis to the acrosome phase (steps 8–14) after 20 days of recovery.

FIG. 12. Advance of spermatogenesis to normalcy 30 days after withdrawal of treatment. Interstitial cells are secretory.

FIG. 13. Normal spermatogenesis in a 78-day-old rat treated with olive oil (terminal control). Interstitial cells are secretory.

PLATE 4

Figs. 14–17. Effects of various treatments on the pituitary glands. Rats were 78 days old at the time of autopsy. Treatment: 250 $\mu\text{g}/\text{day}$ or 1 mg of clomiphene per day, or 5 μg of oestradiol per day for 55 days, beginning on Day 22. Identical areas of the postero-medial angle of horizontal sections of the pituitaries were photographed in all groups for comparison. $\times 1200$.

FIG. 14. The pituitary of a 78-day-old male rat (terminal control): gonadotrophs are intensely stained.

FIG. 15. The pituitary of an oestrogen-treated rat. Gonadotrophs are degranulated. Chromophobes and acidophils are in abundance.

FIG. 16. The pituitary of a rat treated with 250 μg of clomiphene per day. Gonadotrophs are degranulated and are indistinguishable from chromophobes.

FIG. 17. The pituitary of a rat treated with 1 mg of clomiphene per day. Gonadotrophs are degranulated as in Figs. 15 and 16. There is an apparent increase in the number of acidophils.

PLATE I

Facing p. 48

PLATE 2

PLATE 3

PLATE 4