BIOLOGY OF REPRODUCTION 30, 179–187 (1984)

Effects of the Induction of Experimental Cryptorchidism and Subsequent Orchidopexy on Testicular Function in Immature Rats

B. JÉGOU, R. A. PEAKE, D. C. IRBY and D. M. DE KRETSER[1]

Department of Anatomy
Monash University
Melbourne, Victoria, Australia

ABSTRACT

Cryptorchidism surgically induced in 14-day-old rats, was allowed to persist until 35 days when one group was killed to assess testicular function. In a second group the cryptorchid testis was returned to the scrotum surgically (orchidopexy) and subsequently killed at 130 days. A third group remained persistently cryptorchid to 130 days, while in a fourth group two sham operations were performed at 14 and 35 days. At 35 days, cryptorchidism resulted in a significant decline in testis weight due to suppressed spermatogenesis. Sertoli cell function as measured by seminiferous tubule fluid (TF) production after unilateral efferent duct ligation and androgen-binding protein (ABP) production was significantly depressed in the cryptorchid group. Serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were significantly elevated with cryptorchidism but serum testosterone levels were unchanged. Although morphometric measurements showed no change in Leydig cells cross-sectioned area, in vitro human chorionic gonadotropin (hCG)-stimulated testosterone production was significantly increased in the cryptorchid group at higher hCG doses.

Similar changes were found in cryptorchid testes at 130 days except that Leydig cell cross-sectional area was now significantly increased. Orchidopexy at 35 days restored spermatogenesis and fertility during test mating was not impaired. TF production, ABP accumulation and serum FSH levels returned to normal following orchidopexy. Leydig cell function following orchidopexy, as measured by serum LH and testosterone levels, and Leydig cell cross-sectional area, was not different compared to controls. hCG-stimulated in vitro testosterone production following orchidopexy was not different compared to controls, although basal testosterone production was significantly elevated. The study demonstrates that all aspects of testicular function are impaired following cryptorchidism in immature rats but orchidopexy after 21 days restores essentially all aspects to normal.

INTRODUCTION

The results of studies from a number of laboratories have demonstrated that following the induction of cryptorchidism in adult rats, Sertoli cell and Leydig cell function is impaired in addition to the interference with spermatogenesis (Gupta et al., 1975; Rager et al., 1975; Hagenas and Ritzén, 1976; Kerr et al., 1979a,b; Keel and Abney, 1980; Risbridger et al., 1981a,b; Jégou et al., 1983a). In an attempt to determine if these changes were reversible, orchidopexy was performed 10–28 days after the induction of cryptorchidism. However, we found that after only 10 days of cryptorchidism, there was a very poor recovery of spermatogenesis and little recovery of Sertoli cell and Leydig cell function (Jégou et al., 1983b).

Prompted by the studies of Bergh and Damber (1978), who could find no change in Leydig cell size when cryptorchidism was induced in the neonatal period, and in view of the failure of the adult rat testis to recover after cryptorchidism was reversed, we set out to determine if the immature testis behaved in a similar manner. Additionally, during the present study, Karpe and co-workers (1981) reported the restoration of androgen-binding protein (ABP) secretion when cryptorchidism was induced in immature rats and reversed subsequently. This study was designed to evaluate the changes in spermatogenesis, Sertoli cell function and Leydig cell function when cryptorchidism is induced in immature rats and reversed 21 days later.

Accepted August 19, 1983.
Received March 17, 1983.

[1] Reprint requests: Dr. D. M. de Kretser, Dept. of Anatomy, Monash University, Clayton, Victoria 3168 Australia.

MATERIALS AND METHODS

Surgical Procedures

Fourteen-day-old Sprague-Dawley rats were used for this experiment. The rats were anesthetized with ether, and a small incision was made in the abdomen. On both sides the gubernaculum of the testis was cut and the testis was anchored to the inner lateral abdominal wall by a suture passing through the connective tissue of the cauda epididymidis. Due to the fragility of the testes in animals of this age, particular care was taken to avoid any contact with the testes themselves during the operation. In other animals sham operations were performed by opening the abdomen and handling the epididymis. After closure of the incision, both cryptorchid and sham-operated animals were returned to their mothers for a week before they were weaned.

Twenty-one days after the operation (at 35 days of age) the first group of sham-operated and cryptorchid rats was killed for evaluation of testicular function. At the same age, orchidopexy was performed on a second group of rats. The placement of the testes into a scrotal position was achieved by cutting the suture anchoring the testis and epididymis to the abdominal wall and gently pulling them down to the scrotum, where they were secured by a ligature passing through the connective tissue of the cauda epididymidis and the scrotal skin. Sham operations were performed in those rats which were to be left cryptorchid and in those which were serving as sham-operated controls. All the animals of this second group were then killed at 130 days of age. Tubule fluid production and ABP accumulation were measured after 16 h of an unilateral efferent duct ligation (EDL) performed as previously described (Jégou et al., 1983a). Briefly, this involved ligation of the efferent ducts of one testis of each rat 16 h before they were killed, the difference in testis weight between the ligated and unligated testis providing an index of fluid production. After weighing, the testes were homogenized and centrifuged at 105,000 × *g* to provide a cytosol preparation for measurement of ABP by steady-state polyacrylamide gel electrophoresis (Ritzén et al., 1974).

Collection and Preparation of Tissues

The animals were killed by decapitation and blood was collected. After separation, serum was stored at −20°C for hormone assay. The testes and epididymides were collected and prepared for histological observation and measurement of testicular parameters as previously described (Jégou et al., 1983a). In rats killed at 130 days, the numbers of spermatozoa present in homogenates of the epididymis were determined by the technique of Robb et al. (1978).

Morphological Study

The testes of rats in each experimental group (5 rats per group) were fixed by perfusion using a mixture of 5% glutaraldehyde, 4% formaldehyde and 0.05% 2,4,6-trinitrocresol buffered to pH 7.4 with 0.2 M sodium cacodylate, as described by Kerr and de Kretser (1975). Following postfixation in osmium tetroxide, small pieces of testicular tissue were dehydrated and embedded in a mixture of 1:1 Epon and Araldite. Sections (0.5–1 μm) were stained with toluidine blue and examined using a Leitz Orthoplan microscope. The cross-sectional areas of at least 135 Leydig cells per animal, selected at random, were measured using a Leitz-Image Analyser according to methods previously described (Risbridger et al., 1981c).

In Vitro Production of Testosterone

Following decapsulation, hemi-testes from the experimental animals were incubated for 4 h in Kreb's Ringer bicarbonate (KRBG) containing glucose (1 mg/ml) as previously described (de Kretser et al., 1979; Jégou et al., 1983a). Hemi-testes from rats at 35 days were incubated without hCG (basal) and with concentrations of hCG (Pregnyl, Organon) ranging from 0.0005 to 5000 mIU/ml. After 4 h, the incubation media were centrifuged at 800 × *g* and stored until assayed for testosterone.

In the animals killed at 130 days, basal testosterone production and maximally stimulated testosterone production (hCG 700 mIU/ml, a dose shown to result in maximal stimulation, Risbridger et al., 1981c) were assessed in controls, cryptorchid and orchidopexy groups.

Hormonal Measurements

At the time the rats were killed by decapitation, blood was collected, and after separation, the serum was stored at −20°C for hormone assay.

Testosterone: Levels in serum were measured following ether extraction using a radioimmunoassay described previously (Risbridger et al., 1981c). Briefly, the antiserum was raised in sheep against testosterone 3-carboxymethyoxime coupled to bovine serum albumin and cross-reacted with 5α-dihydrotestosterone (98%). The intraassay coefficient of variation ranged between 6–9% and all samples were measured in one assay. Testosterone levels in the KRBG incubation media were assayed without extraction because this had no effect on the results (Risbridger et al., 1981a).

LH and FSH: Serum LH and FSH were assayed using specific double-antibody radioimmunoassays with reagents kindly supplied by the National Pituitary Agency, using the method of Lee et al. (1975). Purified rat LH (NIAMDD-rat -I-6) was used as a standard and tracer for the LH assay. Purified rat (FSH (NIAMDD-rat -I-3) was used as tracer and rat FSH (NIAMDD-rat FSH-RP-1) was used as the standard. The intraassay coefficient of variation for both assays ranged from 5–7% and all samples from the experiment were measured in the same assay.

Fertility Testing

Control rats, cryptorchid rats and rats in whom an orchidopexy was performed at Day 35 were fertility tested at 120 days. For 1 week each male rat was housed with two mature, cycling female rats. Ten days later the females were killed and the number of embryos counted.

Statistical Analysis

The data were analyzed by Student's *t* test and where indicated by analysis of variance and Duncan's multiple range test.

RESULTS

Testis and Epididymal Weight

Three weeks (35 days of age) after the induction of cryptorchidism, testis weight decreased significantly to 69% of controls (Table 1). In those rats in which cryptorchidism was allowed to persist to 130 days the testis weight was strikingly reduced and was equivalent in weight to the testis from control 35-day-old rats. Orchidopexy restored testis weight to normal (Table 1).

No significant difference in epididymal weight was found at 35 days of age in cryptorchid rats. Epididymal weight in cryptorchid rats killed at 130 days was significantly lower ($P<0.001$) in comparison to those of control rats or those in which orchidopexy had been performed at 35 days (Table 1).

Number of Epididymal Spermatozoa and Fertility Testing

There was a significant reduction in the number of epididymal spermatozoa in the cryptorchid rats killed at 130 days (control, $6.84 \pm 0.38 \times 10^6$; cryptorchid, 0). However, in those rats subjected to orchidopexy, recovery was complete ($6.21 \pm 0.52 \times 10^6$).

Fertility testing demonstrated that although mating occurred, none of the cryptorchid rats were fertile, whereas orchidopexy restored fertility to control levels. Control males fertilized 80% of females mated, whereas orchidopexied males fertilized 100% of females. In addition, the number of embryos/female pregnant to the rats subjected to orchidopexy was not different to control rats (controls, 12.5 ± 0.6 embryos/female; orchidopexy, 11.8 ± 0.6 embryos/female).

Histological Studies

Spermatogenesis: The most advanced stage of spermatogenesis was the early spermatid stage (Fig. 1a) in 35-day-old control rats. In the cryptorchid rats there were decreased numbers of spermatids and primary spermatocytes with no observable change in spermatogonia. Many spermatids had pyknotic nuclei and formed multinucleate collections (Fig. 1b). Leydig cells were present in the intertubular tissue in all groups and, although no quantitative studies were performed, they appeared to be more plentiful in the cryptorchid group.

At 130 days the seminiferous epithelium in the cryptorchid group was lined by spermato-

TABLE 1. Effect of cryptorchidism and orchidopexy on testis and epididymal weight and hormonal parameters.

	35 Days of age		130 Days of age		
	Control	Cryptorchidism	Control	Cryptorchidism	Orchidopexy
Testis weight (g)	0.40 ± 0.04*	0.27 ± 0.03[b]	1.68 ± 0.05	0.36 ± 0.06[c]	1.52 ± 0.12
Epididymal wt. (g)	0.07 ± 0.01	0.05 ± 0.01	0.58 ± 0.02	0.23 ± 0.01[d]	0.54 ± 0.02
Serum FSH (ng/ml)	670 ± 51	988 ± 61[c]	319 ± 36	1038 ± 148[d]	349 ± 27
Serum LH (ng/ml)	0.40 ± 0.05	3.9 ± 0.74[a]	0.60 ± 0.10	3.46 ± 0.36[d]	0.80 ± 0.18
Serum T (ng/ml)	1.63 ± 0.20	1.74 ± 0.34	5.20 ± 0.81	3.57 ± 0.61	5.61 ± 1.32

*Mean ± SEM for 5–7 rats/group.
[a-d]Significance of difference relative to control of same age: [a]$P<0.05$; [b]$P<0.025$; [c]$P<0.01$; [d]$P<0.001$.

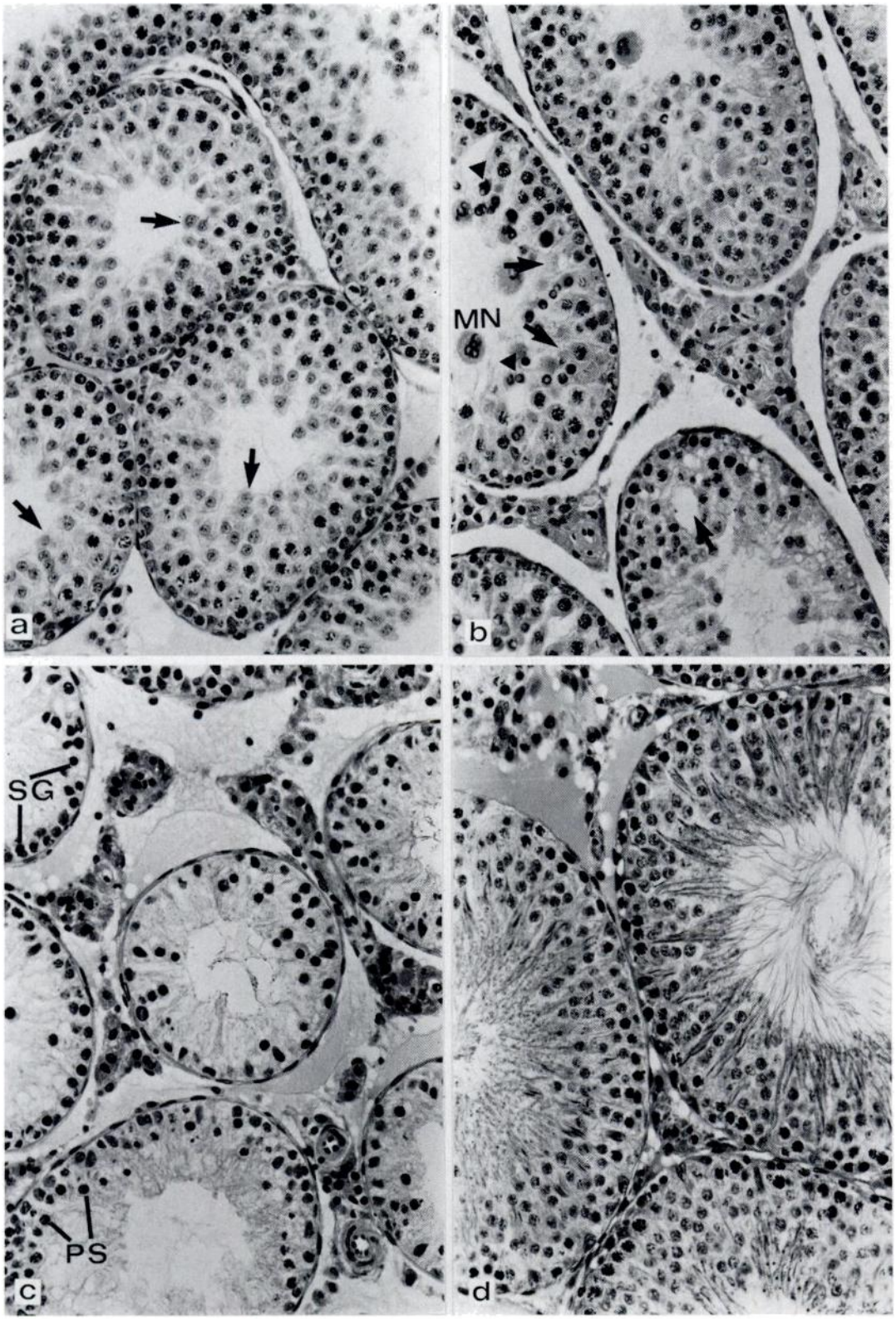

FIG. 1. *a*) Photomicrograph of testis from 35-day-old normal rat. Note most advanced cell type, the early spermatid (*arrows*). X240. *b*) Photomicrograph of testis from 35-day-old cryptorchid rat. Note depopulation of epithelium (*arrows*). Pyknotic spermatocytes and spermatids (*arrowheads*) and multinucleate cells (*MN*). Also note prominent intertubular tissue. X240. *c*) Photomicrograph of testis from 130-day-old cryptorchid rat. Note loss of germ cells from epithelium with sparse retention of spermatogonia (*SG*) and primary spermatocytes (*PS*). X240. *d*) Photomicrograph of testis from a rat at 130 days following orchidopexy at 35 days of age. Note restoration of spermatogenesis.

gonia, a few primary spermatocytes and Sertoli cells. The total number of germ cells was severely reduced (Fig. 1c). In the orchidopexy group full spermatogenesis was restored and no difference was obvious in comparison to controls (Fig. 1d).

Leydig cells: In the morphometric studies no significant difference in Leydig cell cross-sectional area was evident between cryptorchid and control rats at 35 days (Table 2). The size of the Leydig cells increased significantly ($P<0.001$) in all groups between 35 and 130 days of age. However, cryptorchid rats at 130 days showed a significant ($P<0.01$) increase in cross-sectional area in comparison of both control rats and those in which orchidopexy was performed at 35 days (Table 2).

Leydig Cell Function

Serum testosterone and LH levels: No significant changes were found in the serum testosterone levels between any of the groups (Table 1). Serum LH levels were significantly elevated in the cryptorchid rats at 35 days ($P<0.05$) and also at 130 days ($P<0.001$; Table 1). Orchidopexy returned serum LH levels to normal (Table 1).

In vitro testosterone production: No significant difference was found in basal testosterone production in vitro, between control and cryptorchid rats at Day 35 (Fig. 2). However, at low concentrations of hCG there was a significant ($P<0.05$) impairment of testosterone production in vitro by cryptorchid testes which was

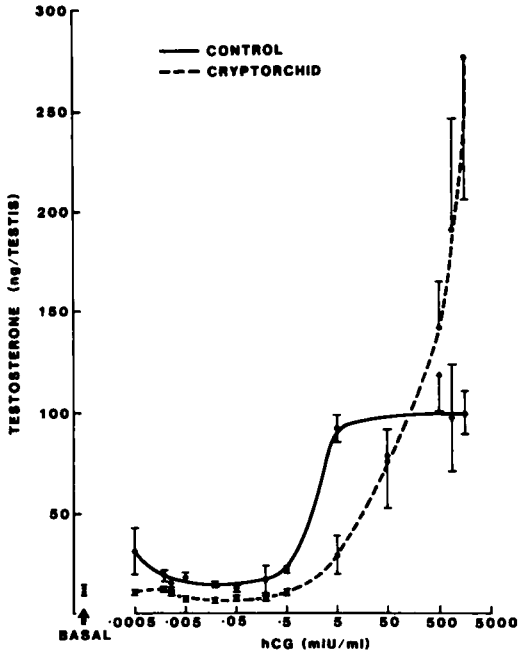

FIG. 2. The effect of increasing concentrations of hCG on in vitro testosterone production during a 4-h incubation in KRBG is shown for immature cryptorchid rat and controls at 35 days. Values represent mean ± SEM for 3 testes per dose of hCG.

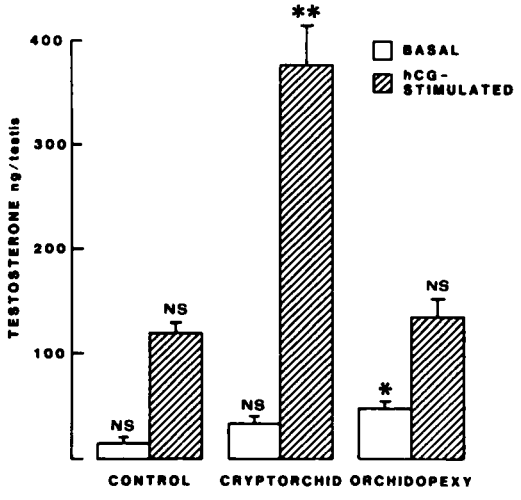

FIG. 3. The effect of cryptorchidism induced in immature rats at 14 days and orchidopexy at 35 days on in vitro testosterone prodcution over 4 h in KRBG. hCG-stimulating dose was 700 mIU/ml and data represent mean ± SEM for 9–12 testes per group. Significance determined by analyses of variance after log transformation of data and subsequent application of Duncan's multiple range test for unequal numbers. $^{*}P<0.05$; $^{**}P<0.01$.

TABLE 2. Effect of cryptorchidism and orchidopexy on Leydig cell size.

Age of rats* (days)	Leydig cell cross-sectional area (μm^2)		
	Control	Cryptorchid	Orchidopexy
35	79.1 ± 0.2	74.9 ± 4.6	- - -
130	110.7 ± 3.7[a]	127.6 ± 5.6[ab]	98.2 ± 4.7

*n=4 rats per group.

[a]P<0.001 compared to size at 35 days.

[b]P<0.01 compared to control at 130 days.

reversed at high concentrations (Fig. 2). Although there was considerable variability in the in vitro testosterone production at doses of 500–5000 mIU/ml of hCG, the levels made by cryptorchid testes were significantly (P<0.05) higher than controls.

In animals killed at 130 days, there was no significant differences in basal testosterone production between control and cryptorchid rat testes, but the testes from rats subjected to orchidopexy showed a greater basal testosterone production (P<0.05; Fig. 3). hCG stimulation resulted in a significant (P<0.01) hyperresponsiveness in the cryptorchid group with peak levels that were three times greater than maximally stimulated controls. In the rats which had an orchidopexy performed, hCG-stimulated testosterone levels were not significantly different from controls although some increased variability was noted. In this group careful checking revealed that the rats showing a greater testosterone production tended to have lower testis weights (data not shown) which reflect incomplete spermatogenic recovery.

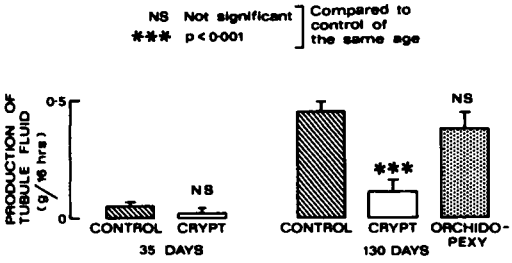

FIG. 4. The effect of cryptorchidism and subsequent orchidopexy in immature rats on the production of tubule fluid at 35 and 130 days of age. Values are mean ± SEM for 4–5 rats/group.

Sertoli Cell Function

Tubule fluid (TF) production: A significant decrease (P<0.001) in TF produciton was noted in the cryptorchid testes of 35-day-old rats (Fig. 4). However, TF production was normal at 130 days in animals in which orchidopexy was performed at 35 days. In those rats in which cryptorchidism was allowed to persist to 130 days, TF production was grossly suppressed to 15% of controls (Fig. 4).

ABP content and production. At 35 days the accumulation of ABP in the testis after EDL was significantly decreased in the cryptorchid testes in comparison to control (Fig. 5). At 130

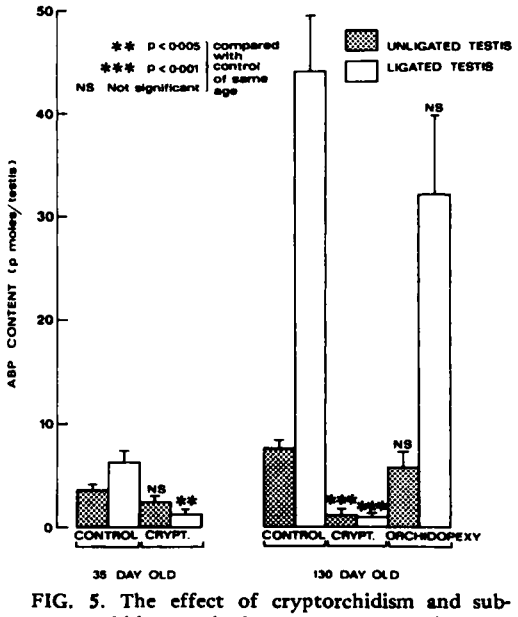

FIG. 5. The effect of cryptorchidism and subsequent orchidopexy in immature rats on the ABP content and accumulation following unilateral efferent duct ligation 16 h previously. Values represent mean ± SEM for 5 rats/group.

days, no significant difference was found in ABP production in the group of rats in which orchidopexy was performed and the age-matched controls (Fig. 5). However, in the rats with persistent cryptorchidism there was a marked reduction in ABP accumulation in comparison to controls ($P<0.001$) and to those rats subjected to orchidopexy (Fig. 5).

Serum FSH levels. This parameter is included in this section because it may indirectly reflect inhibin production by the testis, which has been shown to be suppressed in cryptorchidism (Au et al., 1983). At 35 days the cryptorchid rats showed significantly elevated FSH levels, a state which persisted at 130 days of cryptorchidism (Table 1). However, orchidopexy at 35 days restored FSH levels to control levels when the rats were killed at 130 days.

DISCUSSION

This study demonstrates that cryptorchidism induced in the immature rat before sexual maturation results in a significant impairment in all aspects of testicular function, including spermatogenesis, Sertoli cell and Leydig cell function. The impairment in spermatogenesis and Sertoli cell function confirms the results of a study published by Karpe et al. (1981) during the analysis of the present data. However, to date it has been assumed that Leydig cell function was unaltered in the immature cryptorchid rat since Leydig cell size was normal (Bergh and Damber, 1978). The present data confirm that Leydig cell size is unchanged but demonstrate hyporesponsivity of testicular testosterone production to hCG stimulation at low doses in the immature cryptorchid rat and hyperresponsivity at high doses of hCG. The hyporesponsivity at low doses may be related to a decreased sensitivity of the testis to hCG based on the decline in LH receptor demonstrated on Leydig cells from adult cryptorchid rats. Taken together with the elevated serum LH levels, the study shows that the Leydig cell dysfunction is similar to that present when the mature testis is made cryptorchid (Kerr et al., 1979b; de Kretser et al., 1979). The presence of elevated serum LH levels associated with normal serum testosterone levels suggests the existence of a state of compensated Leydig cell failure virtually identical to the adult cryptorchid testis. In this state, elevated levels of LH are required to enable the testicular output of testosterone to be maintained in the normal range. The failure of Leydig cells from the cryptorchid testis, which are hyperresponsive in vitro to hCG, to maintain normal circulating testosterone levels without the necessity for elevated LH levels may seem paradoxical. However, it is likely that two additional factors contribute to this situation: *1*) decreased blood flow to the cryptorchid testis (Damber et al., 1978), and *2*) decreased levels of LH receptors in cryptorchidism. This view is supported by the findings in vivo that at low doses of hCG, the testosterone response of the cryptorchid testis is subnormal, whereas at high doses of hCG the cryptorchid testosterone response surpasses the control (Risbridger et al., 1981c).

The finding of normal Leydig cell cross-sectional area in the immature cryptorchid testis is of interest in view of the demonstrated hyperresponsivity to hCG stimulation at high doses. It suggests that the total number of Leydig cells may be increased, a parameter which will require confirmation by morphometric analysis. This pattern contrasts with that in the adult cryptorchid testis where hypertrophy of the Leydig cells is observed. While it is clear from experiments in adult rats involving unilateral testicular damage that local factors are involved in the Leydig cell changes (Risbridger et al., 1981a,b,c) the increase in Leydig cell size from 35 days to 130 days suggests that LH stimulation may be required to facilitate the hypertrophy.

The results in the present study also confirm that orchidopexy prior to sexual maturation can reverse the germ cell degeneration and restore spermatogenesis (Karpe et al., 1981). This contrasts with the failure of spermatogenesis to recover following periods as short as 10 days of cryptorchidism in the adult (Hayashi and Cedenho, 1980; Jégou et al., 1983b). This seems likely to result from the sparing of spermatogonia from damage in the immature cryptorchid testis, which is consistent with the observations of Moore (1924) who noted retention of spermatogonia. Surprisingly, in 130-day-old cryptorchid rats, preservation of spermatogonia was considerably greater than when cryptorchidism was induced in the adult state (Jégou et al., 1982b).

The present study also demonstrates that the changes in both Sertoli cell and Leydig cell function induced by cryptorchidism are reversible. It seems likely that this reversal is not simply the result of the restoration of the scrotal position since the similar experiment of

orchidopexy in the adult did not reverse the changes in Sertoli cell and Leydig cell function (Jégou et al., 1983b). The important difference between the two experiments is that spermatogenesis was restored following orchidopexy in the immature cryptorchid rat but not in the adult. This observation suggests that it is not the cryptorchid position that influences Sertoli cell and Leydig cell function but rather the requirement for normal spermatogenesis to restore their function. It is thus possible that an interaction exists between the three major cell types within the testis, namely germ cells, Sertoli cells and Leydig cells. Evidence for germ cell-Sertoli cell relationships is rapidly accumulating from those studies utilizing isolated segments of seminiferous tubules (Parvinen et al., 1980; Lacroix et al., 1981). Evidence for a relationship between the seminiferous epithelial cycle and Leydig cell function is also now available from the study of Bergh (1982). He showed that the cross-sectional area of Leydig cells also varies with the stage of the seminiferous cycle. This information, together with that from our studies of Leydig cell function (Rich et al., 1979; de Kretser, 1982) associated with spermatogenic damage, suggests that the two compartments of the testis exert a significant influence on the function of one another.

ACKNOWLEDGMENTS

This study was supported by grants from the National Health and Medical Research Council of Australia and the Ford Foundation. The expert technical assistance of Richard Allen, Ann Davies, Enid Pruysers and Sue Ellis is gratefully acknowledged.

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