MALE INFERTILITY

It is only in the last fifteen years that physicians have been more aware of the contribution of male infertility to the childless couple. Even at this it is not uncommon to find the problem poorly investigated and managed. I think this has partly stemmed from persistent gaps in our knowledge of normal and abnormal testicular function and that the subject is badly covered in most medical school curricula. The incidence of male infertility as a cause of barren marriages has been put as high as 50%. Thus an early knowledge of the quality of the semen is essential in the investigation of the childless couple. It turns out that even when male dysfunction is shown in half these cases there is also dysfunction in the female[2] and so investigations should continue in parallel.

To my knowledge the problem has not been well-documented in Saudi Arabia. The Department of Pathology in the University receives many of the testicular biopsies done by urologists in the region. But the incedence of male infertility has not compared with other centres in the world. I would also suggest that we are only seeing the tip of the problem in the Saudi Arabia and I believe the case for a thorough evaluation of male infertility is important and such studies are urgently needed.

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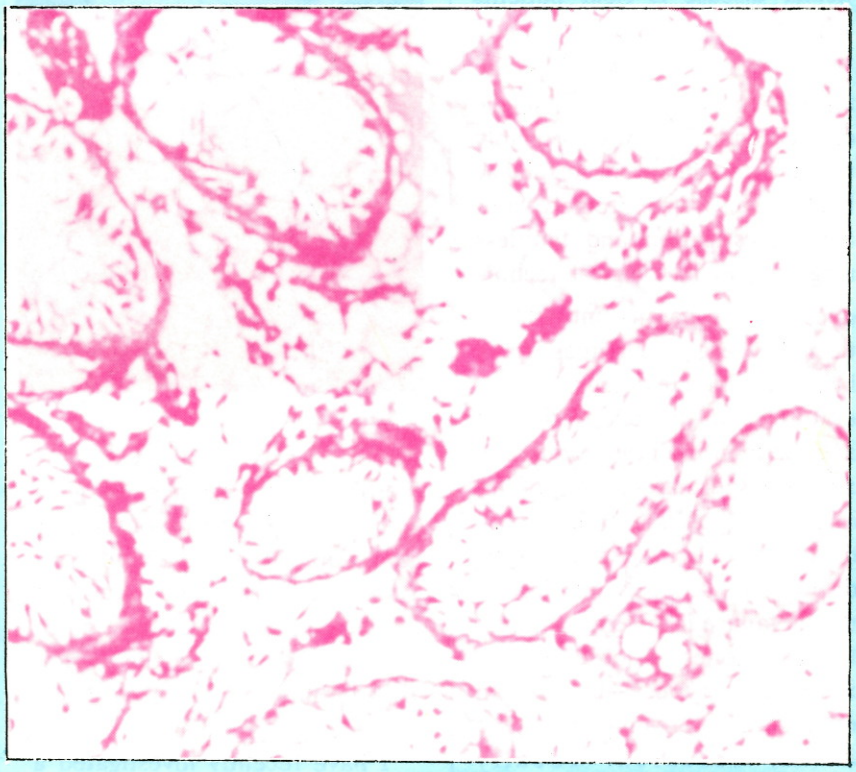
When should the male be investigated? Macleods careful studies in 1951[3] indicated that a man has a reasonable chance of fertility with a sperm density that exceeds 20 million/ml, with more than 30% indicated that a man has a moving actively within four hours of production in a volume of at least 1.5 ml. Occasionally a man can be sterile with a normal sperm count due to high levels of anti-sperm antibody[4]. In this region one commonly finds the patient with azoospermia or oligospermia (i. e. < 20 million/ml) referred by the urologist after semen analysis and testicular biopsy have already been done. The laboratory facility for semen analysis appears to exist in most hospitals, although technically simple considerable subjective observer error can enter into the assessment of mobility, sperm density and morphology. In present circmstances at least three specimens should be examined on different occasions before oligospermia should be accepted.

A thorough history may by itself provide the necessary clue to the presence of a causative factor responsible for one of the well-defined disorders affecting testicular function: endocrine disorder (e. g. diabets mellitus, pituitary disease or thyroid disease) genetic-developmental disorders (e. g. Klinefelters syndrome xxy, cryptorchidism) neurologic disorders, sexual dysfunction, anatomical abnormalities (e. g. hypospadias) and exposure to toxic substances (e. g. alcohol, radiation).

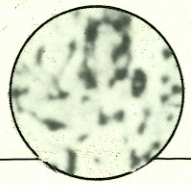
In the physical examination special attention is paid to the size of the testes in the scrotum, the epididymis is examined for structural irregularities which might indicate a block-a surgically relievable cause of azoospermia. The patient is examined standing to rule out the presence of a varicoele. Rectal examination is conducted to uncover prostatic or seminal vesicale disease.

At this stage one should be able to direct the investigations to uncover the disorder of testiculer function in the patient. These disorders are best classified according to the circulating level of gonadotrophins in serum (Table I). Not included in this classification are neurologic disorders, sexual dysfunction myotonia dystrophica, physical and chemical agents, vascular abnormalities and the important group of bacterial and traumatic damage causing primary testicular failure.

The absence of radioimmunoassay services in this region to measure the basic hormonal profile i. e., serm LH, FSH, pro-



Sertoli cell only syndrome



lactin and plasma testosterone has often made referral elsewhere necessary. Consequently there has been an understandable tendency by surgeons to go ahead with testicular biopsy in order to rule out an obstructive azoospermia or acquired testicular disease of a treatable kind e. g. tuberculosis. Unfortunately this means that patients with low LH, FSH levels are subjected to unnecessary biopsy as these are the cases of secondary testicular failure, the cause lying outside the testes. Unless the clinical evidence of block or acquired testicular disease is clear patients with testicular disorders should first have a hormonal profile. In this setting raised or nomal levels of LH and FSH will probably indicate the need for testicular biopsy. This is an extremely valuable investigation and faultless surgical and histological techniques are of paramount importance. These techniques have been described in detail in the literature[5]. An infectious disease may be identified but commonly arrested spermatogenesis of an idiopathic type is found. In particular we have seen the syndrome of adult seminiferous tubule failure in several patients, the commonest disorder of the idiopathic type. This is an extremely interesting field for future research. Ideally chromosomal analysis of the biopsy specimen should be undertaken and evaluation of steroidogenic enzymes. In general no adequate form of therapy is available for adult seminiferous tubule failure. The question arises as to whether it is a more common problem in this region than in other regions of the same latitude.

I have recently investigated a patient with possible Sertoli cell Only Syndrome. He had azoospermia and elevated gonadotrophins with normal androgenic function of the testes. The Karyotype was normal. Testes were of normal size but the seminiferous ubules may contain only Sertoli Cells. There was no peritubular fibrosis or hyalinisation. Unfortunately, there is no treatment for this disorder but this is the great research spur to the clinical investi gation faced with his patient.

Normal or low levels of LH, FSH may imply hypothalamic-pituitary failure. These patients usually have small testes and there is no indication for testicular biopsy. To confirm that the lesion lies in the hypothalamus (Kallman's Syndrome i. e. isolated LH-RH deficiency) or the pituitary gland a clomiphene citrate stimulation test is administered, 100 mg daily for five days. This substance appears to occupy receptor sites for testosterone (and oestrogen) in the hypothalamus and thus cause a no response whereas in hypothalamic disease significant elevation of serum LH and FSH occurs. I am investigating one such patient at the present time, he has azoospermia and very small testes with low serum FSH, LH levels. In these cases a pituitary tumor is a possibility and lateral and AP views of the sella tursica and visual field examination value. In pituitary disease there is

release of gonadotrophins in the normal subject. A normal response is a doubling of the LH level from the baseline value. If this is not achieved hypothalmic-pituitary failure is strongly indicated. A luteinising hormone releasing factor (LH-RH) test is then administered 100 ug of LH-RH is given I.V, and samples at 20 and 60 mins are compared with the baseline is essential. Prolactinomas are rare in males and are usually accompanied by galactorrhoea but they are an eminently treatable cause of male infertility and this is why a serum prolactin is part of the hormonal profile. Kallman's syndrome (sometimes accompanied by anosmia) is a cause of infertility which should respond well to the administration of human chorionic gonadotrophin (LH activity) and human menopausal gonadotrophin (LH and FSH activity) to maintain normal leydig cell production of testosterone and normal spermatogenesis. Chronic therapy with LH-RH is being undertaken but the long term success is not yet known.

Future research is now concentrating on the detection of specific steroid enzyme deficiencies in the Leydig cell and on the interesting phenomenon of an androgen binding protein produced by the Sertoli cell. With the new understanding of subclinical hypothalamic-pituitary failure the physician is on the threshold of new advances in developing rational therapy for patients with inadequate sperm production.

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TABLE I
DISORDERS OF TESTICULAR FUNCTION

Low LH, FSH Levels	Raised LH, FSH Levels	Normal LH, FSH Levels
Isolated LH-RH deficiency (hypogonadotrophic hypogonadism)	Congenital adsence of testes	Adult Seminiferous Tubule Failure
or Kallman's syndrome.	Testicular ectopia	
panhypopituitarism	Klinefelters syndrome	Post Orchitis Oligospermia
Isolated LH deficiency (the fertile eunuch, normal FSH)	Ullrich - Turners Syndrome (Male Turners Syndrome)	
Prader - Willi Syndrome	Reifenstein's syndrome	
Lawrence Moon-Biedl Syndrome	Sertoli Cell Only Syndrome	
Alstrom Syndrome	XX Syndrome (Clinical appearance of Klinefelters, Y chromosome presumed to be translocated to an autosome).	
Congenital adrenal hyperplasias (precocious pseudopuberty with small testes).	Gonadal dysgensis (Streak gonads)	
Oestrogen producing adrenal cancer	Congenital deficiencies of steroid enzymes.	