Conclusion

Easy access to a unit which provides both medical and psychiatric care improves the management of disturbed elderly patients in hospital. Patients at home in a disturbed mental state and suffering from organic disease or brain damage may also need swift admission to hospital. Admission to a psychiatric hospital is rarely appropriate or immediately feasible and a psychogeriatric acute unit with full diagnostic and therapeutic facilities clearly has a place in a general hospital service.

Dealing with the problems presented by disturbed patients admitted to such a unit proved to be within the competence of general trained nursing and medical staff, and psychiatric help, willingly given on request, was only occasionally needed. The interest of the staff in these patients increased and opened up a new dimension in geriatric medicine. To try to run a geriatric department now without an acute psychogeriatric unit would be unthinkable. Knowing that patients can quickly be transferred, ward staff, uneasy at first in trying to deal with psychiatric disturbance, are now confident, and they feel that they can manage almost any patient.

It was a relief to find that the number of long-stay beds occupied by patients discharged from the psychogeriatric ward was much smaller than expected. It was also pleasing to find that the work of the ward was both interesting and stimulating and that it was one of the busiest and most effective of the hospital admission units, with about 150 admissions annually to 23 beds. General practitioners and consultants in the area all know about the unit and that a bed can always be obtained in an emergency. It provides for the psychogeriatric needs of a population of 340,000, has been effective in the management of a distressing group of patients, and forms one of the essential components of a service concerned with the care of the elderly.

I would like to thank Mr. A. J. Dunning, Director of the Computer Centre, Teesside Polytechnic, for his invaluable help in presenting the statistics; Mrs. Dean, Mrs. George, and Mrs. Hill for clerical help; the consultant psychiatrists of St. Luke's Hospital; the nursing staff of Cleveland Ward; and sister E. M. Schofield and Dr. Frank Begg for their enthusiasm and support.

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Hospital Topics

Testicular Biopsy in Evaluation of Male Infertility

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Summary

Testicular biopsy findings in 100 infertile men were correlated with the clinical findings. Mild or moderately severe tubular lesions were seen in 57 cases and severe changes in 43. Clinical examination and semen analysis were no guide to the severity of the testicular lesion. Though patients with normal sized testes more commonly had mild tubular lesions, many were severe. Patients with small testes more often had severe lesions but some had only mild tubular changes. Biopsy findings in both aspermic and oligospermic patients ranged from normal to a complete loss of germinal tissue.

Testicular biopsy is advocated in infertile men for the complete assessment of the case and for identifying those which are potentially treatable. Patients with a severe lesion can be spared further investigations. The choice and results of treatment are discussed, particularly the surgical treatment of varicocele or obstruction. Only patients with a mild or moderate testicular tubular lesion should participate in future trials with drugs for male infertility.

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Introduction

At present there is little hope of finding the cause or of treating most cases of infertility in otherwise normal men. Surgery offers some hope for a carefully selected few, but otherwise no treatment has yet been shown to produce a consistent and prolonged improvement in sperm production. Nevertheless, new drugs are always coming forward and it is important to be able to identify the patients who may benefit from them.

Testicular biopsy in infertile men was first advocated by Charny[1] to distinguish cases of obstructive aspermia from non-obstructive, to classify cases of oligospermia, and to aid prognosis. Its use as a diagnostic procedure has not, however, been universally accepted. Hanley[2] found it of no value as a routine procedure, Scott[3] recommended it only in cases of aspermia, while Ellis[4] and Garduno and Mehan[5] have used it in a wider context. The study reported here was done to assess the value of testicular biopsy as an addition to clinical evaluation.

Patients and Methods

One hundred successive patients who had a testicular biopsy during the investigation of their infertility were reviewed. Patients presenting to endocrinologists for the investigation of hypogonadism were excluded from the study. All the patients were in good general health. A past history of maldescended testis, venereal disease, mumps, and other causes of orchitis was sought, and details of both past and current medications were recorded. Two independent observers examined each patient for masculine appearance, testicular size and consistency, and the presence of varicoceles and herniae. At least two samples of semen were examined for volume, sperm concentration, motility, morphology, and fructose concentration. Patients with abnormal semen were offered testicular biopsy as a means of reaching a more definitive diagnosis.

The biopsy specimens were taken under general anaesthesia through a small incision into the stretched scrotum, deepened into the visceral tunica albuginea. The protruding tubules were amputated with scissors, giving a tissue specimen of about 2 mm in diameter. This was fixed immediately in mercuric formol saline. Bouin's solution was used in some cases. It gave a slightly better histological preparation, but the added complications made it not worthwhile for routine diagnostic work. Preparations were stained with haematoxylin and eosin, and in severely abnormal cases special stains for collagen and for elastic fibres in the tubular tunica were helpful.

Hormone assays were not available for patients seen in the earlier part of the study. Testosterone-like substance (TLS) measured by competitive protein binding[6] and luteinizing hormone (LH) assayed by double antibody radioimmunoassay[7] were estimated in 53 consecutive patients. Measurement of follicle stimulating hormone (FSH) was not available at the time of the study.

Clinical Findings

Out of the 100 patients 98 had a normal masculine appearance and two appeared eunuchoid. Three had only one scrotal testis, the other having been removed—in two patients because of maldescent and in one patient after torsion. In addition, one patient had a small testis (1 cm in length) in the inguinal canal. An external measurement of 4 cm was taken as the lower limit of length for a normal testis. Clinically normal (bilateral) testes were present in 51 patients, one or both testes were abnormal in 47, and there was a normal solitary testis in two.

There were 55 patients with oligospermia—32 had sperm counts of less than 5 million/ml, 11 of 6-10 million/ml, and 12 of 11-20 million/ml. Motility at two hours was rarely greater than 50%. Abnormal forms constituted 5-25%.

Possible Aetiological Factors—21 Patients had a varicocele; three had had bilateral orchidopexy for maldescended testis; four had had hernia repairs; one had had mumps orchitis; one had schistosomiasis, and a calcified ovum was found in the testicular biopsy; and one had bilateral absent vasa, confirmed by absence of seminal fructose.

Hormone Assays.—Normal TLS and LH values were found in 48 of the 53 patients in whom hormone assay was carried out. Two had decreased levels of TLS and increased levels of LH, and three had decreased TLS with normal LH values.

Chromosome Analysis.—All six patients, including the two with eunuchoidal appearance, in whom the karyotype and buccal smear were examined showed normal male patterns.

Histological Findings

The biopsy specimens were examined without knowledge of the sperm count, testicular size, or other clinical details. The findings were classified according to the following seven categories, arranged in order of loss of germinal epithelium.

(1) *Normal Appearance.*—(Fig. 1, 5 cases.) Tubular diameter 200 μm with thin basement membrane and tunica propria. Normal germinal epithelium showing orderly progression from spermatogonia to spermatocytes with groups of spermatids and mature spermatozoa. There was a distinct lumen. Sertoli cells were compressed between the germinal cells and were not easily seen. Clumps of large pink Leydig cells, often containing Reinke crystalloids, lay between the tubules.

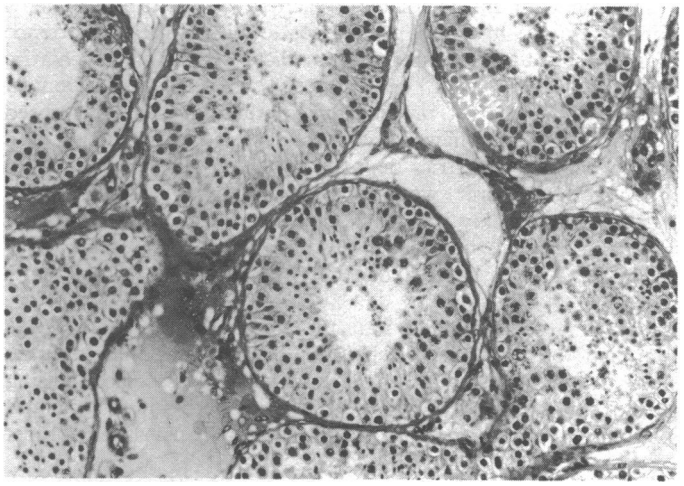

FIG. 1—Normal testicular biopsy appearances. (H. and E. ×130.)

(2) *Tubular Blockage.*—(Fig. 2, 28 cases.) In 19 cases the tubular diameter was normal (200 μm) and in nine cases it was 80-160 μm. The epithelium was cellular with all stages of spermatogenesis, including mature sperms, but without the normal orderly arrangement. The central lumen was lost. In places there was a loose network of precursor cells. Elsewhere the central area of the tubule appeared more cellular than the periphery owing to the jumbled desquamated cells. Leydig cells were normal. Cases were assigned to this group only if half or more of the tubules were affected. Occasional blocked tubules were seen in some cases of hypoplasia.

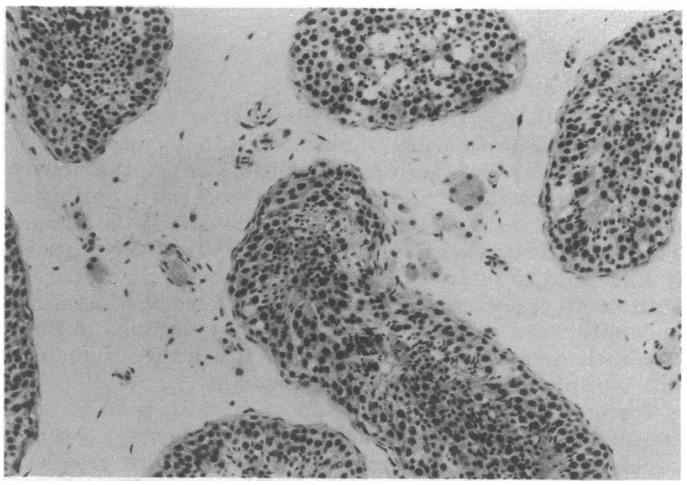

FIG. 2—Testicular tubular blockage. (H. and E. ×130.)

(3) *Hypoplasia of the Germinal Epithelium.*—(Figs. 3, 4, and 10, 46 cases.) In 29 cases the tubular diameter was normal and in 17 cases it was 80-160 μm. There was orderly progression towards sperm production but the cellularity of germinal epi-

thelium was reduced at all stages. The least affected cases showed only a slight quantitative change from normal. In more severe cases only scanty precursors and sperms were seen among clearly visible Sertoli cells. The hypoplasia was classified as mild in 23 cases and severe in 23. The nine worst affected cases showed no sperms at all. All had normal Leydig cells.

(4) *Germinal Cell Arrest.*—(Fig. 5, one case.) In this case the tubular diameter was normal and the germinal epithelium was normal up to the spermatocyte stage. No spermatids or sperms were present, despite much mitotic activity. Leydig cells were normal.

(5) *Sertoli Cells Only.*—(Figs. 6 and 10, 15 cases.) The

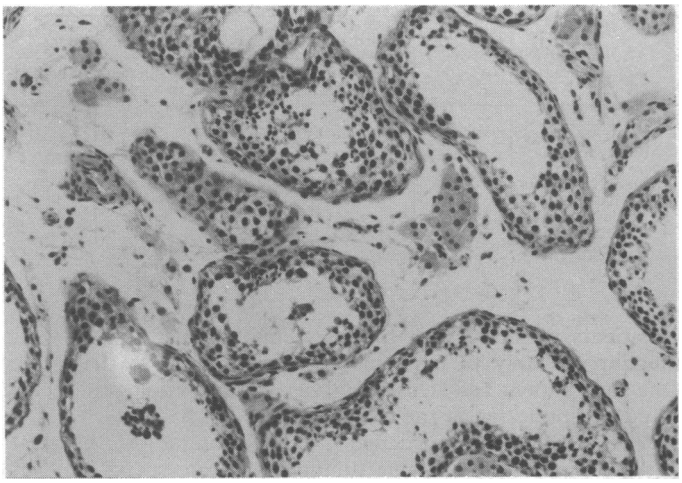

FIG. 3—Mild hypoplasia of the germinal epithelium. (H. and E. ×130.)

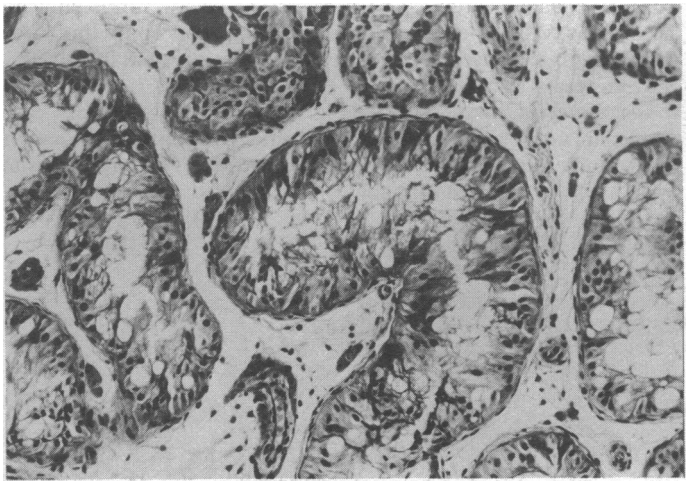

FIG. 6—Sertoli cell only appearances. (H. and E. ×130.)

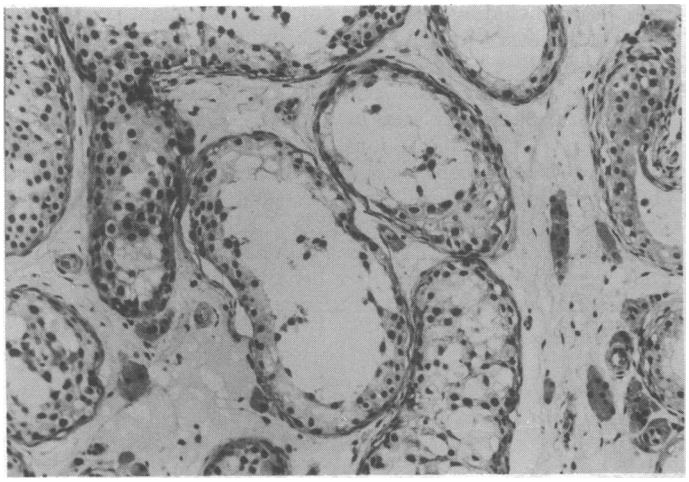

FIG. 4—Severe hypoplasia of the germinal epithelium. (H. and E. ×130.)

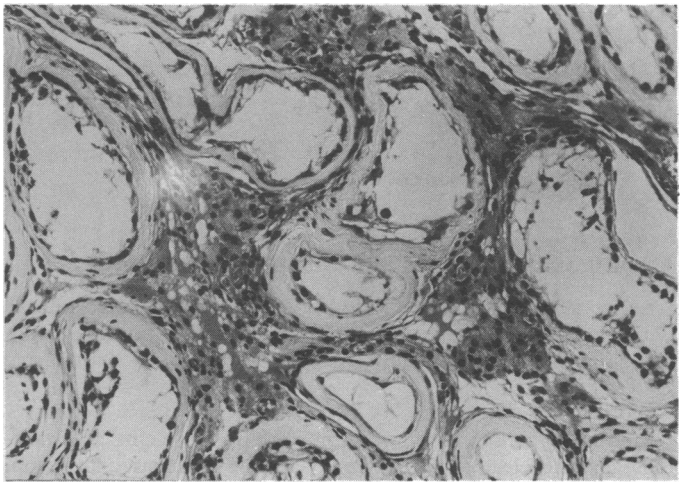

FIG. 7—Tubular hyalinization with thickened basement membrane. Leydig cells are increased. (H. and E. ×130.)

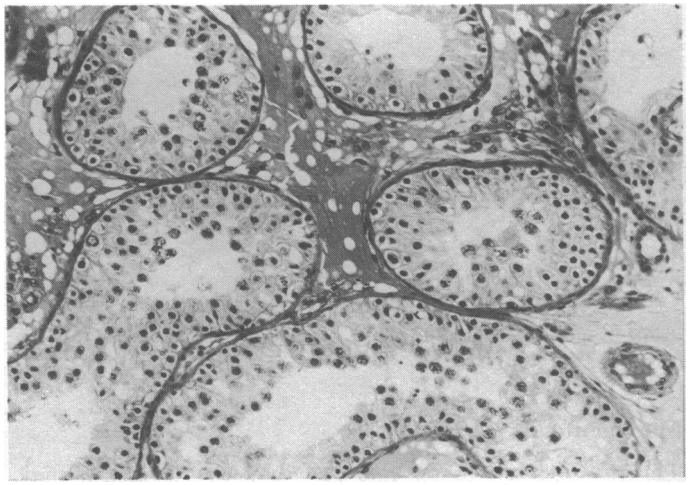

FIG. 5—Germinal cell arrest. There is interstitial oedema. (H. and E. ×130.)

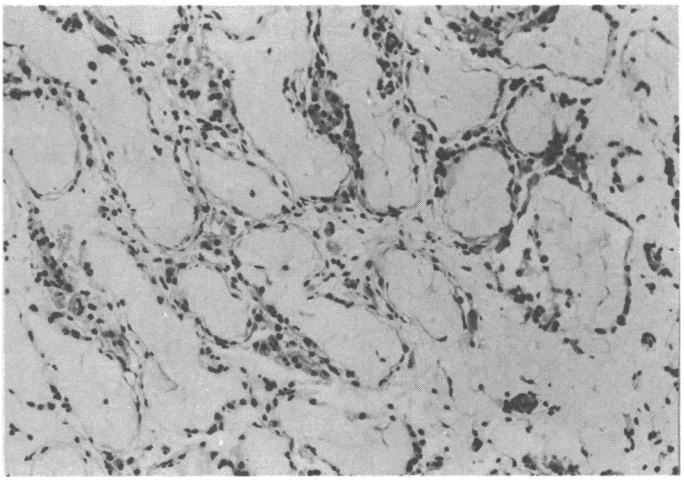

FIG. 8—Tubular hyalinization with tubular "ghosts." (H. and E. ×130.)

tubules, 100-150 μm in diameter, were lined by a single layer of elongated, wispy, pink Sertoli cells. The Leydig cells were normal in 11 cases and reduced in size and number in four. In three cases with normal Leydig cells and in three with reduced Leydig cells the tubular basement membrane was thickened.

(6) *Tubular Hyalinization.*—(Figs. 7 and 8, four cases.) In this probably heterogeneous group the tubules were 60-100 μm in diameter with a much thickened basement membrane and tubular collagenization. The presence of elastic fibres showed that puberty had been reached.[8] The germinal epithelium was lost. Leydig cells were decreased in one case, normal in another, and increased in two.

(7) *Leydig Cell Tumour.*—(Fig. 9, one case.) In this case irregular groups of large pleomorphic eosinophil cells, with large nuclei and increased mitoses, lay in open fibrous tissue with a scattering of lymphocytes. No tubules were seen.

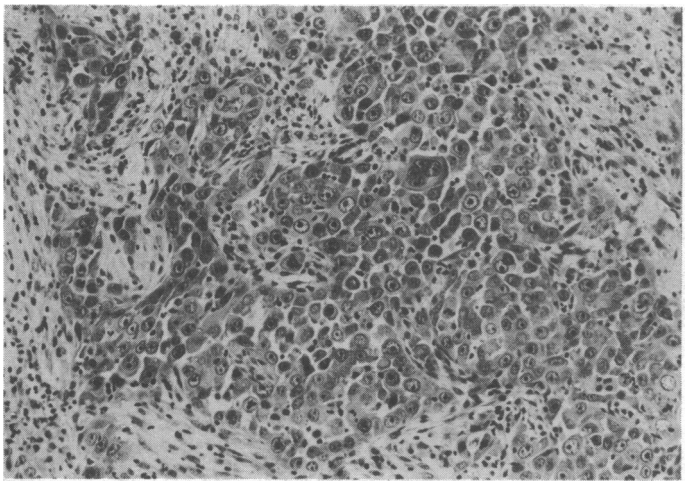

FIG. 9—Leydig cell tumour. (H. and E. × 130.)

Correlation of Clinical and Histological Findings

The cases were considered in four clinical groups—oligospermia with normal-sized testes, oligospermia with abnormal testes, aspermia with normal-sized testes, and aspermia with abnormal testes.

Most of the categories of histological findings were represented in each clinical group (table I). Therefore clinical groupings gave no clear guide to the severity of the testicular lesion. While patients with normal-sized testes more commonly had mild tubular lesions, many had severe lesions. Likewise, though patients with abnormal testes more commonly had severe lesions, some had only mild tubular lesions. Semen analyses correlated with the biopsy findings even less well, since histological appearances ranging from normal to complete loss of germinal epithelium were seen in cases of both aspermia and oligospermia.

TABLE I—*Correlation between Clinical Findings and Histological Appearances in 100 Patients*

Histological Appearances	Total (n = 100)	Normal-sized Testes		Abnormal Testes	
		Oligospermia (n = 35)	Aspermia (n = 17)	Oligospermia (n = 20)	Aspermia (n = 28)
Mild/moderate:					
Normal	5	2	1	1	1
Tubular blockage	28	16	5	3	4
Germinal cell arrest	1	—	1	—	—
Hypoplasia-mild	23	11	7	5	—
Severe:					
Hypoplasia-severe	23	4	2	9	8
Sertoli cell only	15	1	1	1	13
Tubular hyalinization	4	1	—	1	1
Leydig cell tumour	1	—	—	—	1

The clinical and histological findings in cases of varicocele were also correlated (table II). A similar spread of mild and severe lesions was seen, with more mild lesions occurring in patients with normal-sized testes and more severe lesions in patients with abnormal testes.

TABLE II—*Correlation between Clinical Findings and Histological Appearances in Patients with Varicoceles*

Histological Appearances	Total (n = 21)	Normal-sized Testes		Abnormal Testes	
		Oligospermia (n = 10)	Aspermia (n = 2)	Oligosperami (n = 4)	Aspermia (n = 5)
Mild/moderate:					
Tubular blockage	7	4	2	1	—
Mild hypoplasia	6	5	—	1	—
Severe:					
Severe hypoplasia	5	—	—	2	3
Sertoli cell only	2	—	—	—	2
Tubular hyalinization	1	1	—	—	—

Patients with aspermia but only mild tubular lesions were thought probably to have an obstruction distal to the testis. One such patient had schistosomiasis, but no aetiological factor could be implicated in the others.

A testicular biopsy specimen is a small sample of a bilateral organ. It may show variable tubular appearances (fig. 10) but in most cases it will be representative of the whole organ. A few biopsy specimens in which the findings were classified as "Sertoli cell only" contained occasional tubules with hypoplastic germinal epithelium. A large number of those showing hypoplasia, including some in which it was slight, contained scattered tubules with only Sertoli cells. It seems probable that the Sertoli-cell-only appearance is the end-stage of more than one pathological process. Germinal cell aplasia is a misnomer.

Stromal oedema was seen in 17 cases—eight with mild and nine with severe tubular lesions. There was no association with varicocele. Leydig cells were normal in 92 of the 100 cases. They were increased in four cases—one with a Leydig cell tumour, one with tubular blockage, and two with tubular hyalinization. In one of the cases of hyalinization the hormone levels were normal, and in the other the TLS values were low and the LH values normal. The five patients with low TLS values all had severe lesions.

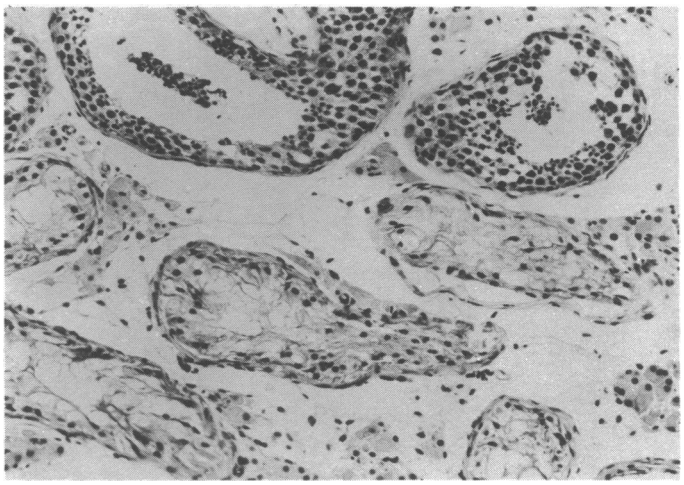

FIG. 10—Varied appearances within same biopsy specimen. Above are mildly hypoplastic tubules, below are tubules with Sertoli cell only appearance. (H. and E. × 130.)

Management

The management of patients attending the infertility clinic included inquiry into habits that might affect spermatogenesis

and conception, such as the type of underwear worn and the optimal frequency and timing of intercourse. Further measures were deferred for a time in patients needing advice on these matters. No treatment was indicated for patients with absent vasa or for those who had severe hypoplasia, Sertoli-cell-only tubules, or tubular hyalinization.

SURGICAL TREATMENT

Ligation of Varicocele.—Twenty-one patients had a left varicocele, and six of these had aspermia. In 14 of the 15 who had oligospermia the varicocele was ligated, irrespective of the degree of oligospermia; in 12 the large spermatic veins in the inguinal canal were ligated and divided; and in two prominent varicosities surrounding the testis were also ligated and divided. The sperm concentration returned to normal in five patients but there was little improvement in motility. Two of these five patients fathered a child. In six patients neither sperm concentration nor motility improved but one of the six fathered a child. In two patients sperm concentration slightly improved (though less than 10 million/ml) but motility was unchanged. One patient was lost to follow-up. Two patients with aspermia underwent ligation of a varicocele because symptoms were attributed to it. Neither of these patients nor those with small testes or severe tubular lesions showed any increase in sperm count after ligation.

Epididymovasostomy.—Nineteen patients with aspermia had mild tubular lesions. Of these, 13 were explored and active sperms were found in the head of the epididymis in 10, and these 10 underwent epididymovasostomy. In one the sperm count rose to normal and his wife became pregnant; in two others the postoperative sperm count showed severe oligospermia, which did not improve further.

Orchidectomy.—This was carried out on the patient with a Leydig cell tumour. He remained well after three years.

HORMONE TREATMENT

Clomiphene.—Eleven oligospermic patients were given clomiphene 100 mg daily. There were no significant changes in either sperm concentration or motility in 10 patients. The count became normal in one patient, but he did not father a child.

Human Chorionic Gonadotrophin (HCG).—One patient with aspermia, small testes, and normal hormone levels had received HCG elsewhere without effect. Of the two patients with evidence of secondary hypogonadism one with severe oligospermia (1 million/ml was given HCG with a resultant improvement in sperm concentration to 4-7 million/ml and in motility from 5% to 20-30% (his wife became pregnant) and the other, with aspermia, was given testosterone only.

Discussion

In the present state of knowledge and of therapy the classification of testicular lesions remains descriptive. We have tried to correlate clinical findings with the extent of the tubular changes. Such a correlation would be most helpful to clinicians, since a way of distinguishing those patients who have potentially treatable testicular lesions is needed.

Mature sperms in considerable numbers are seen in biopsy specimens that show normal tubules, tubular blockage, or moderate hypoplasia. The fault in germinal cell arrest is not well understood, but germinal cell precursors are present and functioning up to a certain stage. These lesions may be regarded as potentially treatable.

Severely hypoplastic testes with small tubules and scanty germinal epithelium are probably incapable of regeneration from the remaining spermatogonia. Those with Sertoli-cell-only tubules or tubular hyalinization have lost the germinal epithelium and so have lost the ability to regenerate. These cases are among the severely affected, and further investigation and treatment of them seems not worthwhile. They form an important proportion of the whole: 43 out of 100 cases in this study.

Clinical examination and semen analysis give insufficient information on which to plan rational treatment. We used the lower limit of normal testicular size (4 cm) as a useful division between "normal" and "abnormal."[9] This measurement may lack the precision of determinations of testicular volume but it is the simplest screening test for adults. Our study has shown that normal-sized testes may be associated with severe tubular lesions and that further treatment for infertility in such cases is of no value. Conversely, when tubular changes are slight treatment may be successful even in patients with small testes and very abnormal sperm counts.

Surgical treatment is largely limited to ligation of a varicocele or to bypass procedures for obstruction.[2] We have singled out patients with varicoceles from the remainder because it is in them that surgery probably has the best chance of success. Dubin and Hotchkiss[10] found it increased the sperm count in 68% of cases and improved fertility in about 30%, but success was achieved only in patients with mild tubular lesions. We think that testicular biopsy carried out either before or at the time of varicocele ligation would have considerable prognostic value, and in those patients with severe tubular lesions several months of needless waiting for treatment destined to be ineffectual would be saved. Though improvement in patients with obstruction is less likely, epididymovasostomy results in the restoration of fertility in a small number of cases. Testicular biopsy would indicate which patients with aspermia have mild lesions and thus were possible candidates for epididymovasostomy. Biopsy will not distinguish between cases of obstruction due to acquired and those due to congenital causes.

Apart from these surgical procedures, there is little in the way of therapy that may confidently be expected to improve spermatogenesis in an apparently normally masculinized man. The value of human chorionic gonadotrophins in hypogonadotrophic, hypogonad patients is well established.[11] Our patients were selected in that they all presented with infertility rather than other endocrine disorders, and over 90% of those in whom hormone assays were carried out had normal values. The use of vitamins, loose-fitting underwear, and cold baths all have their advocates, but part of the disillusionment with these treatments must be due to the false assumption that similar degrees of oligospermia have the same potential reversibility.

The assessment of the efficacy of any new drug is possible only after correct selection of patients about to receive it. A large admixture of untreatable cases will obscure any gains and add to the complications and cost. Progress in the study of male infertility will remain slow unless the maximum information is obtained from each patient and critically examined. We believe that testicular biopsy has an important part to play in this.

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