The commonest category of men with fertility problems are those where semen analysis is abnormal but there is no defined cause for the problem (e.g. WHO categories: idiopathic oligozoospermia, idiopathic teratozoospermia and idiopathic asthenozoospermia). These account for 1345/6682 (20%) men in the WHO series (Table 1.2). If testicular biopsy is performed, damaged spermatogenesis may be confirmed but in general there are no specific features and the underlying nature of the abnormality is as yet poorly defined. Nevertheless, because these problems are common and the demand for help is great many clinicians will prescribe treatment and there have been many claims that a particular treatment regimen has good effect. However, to date most controlled clinical trials have demonstrated no benefit.

The fundamental problem is that descriptions of abnormalities on semen analysis are taken as diagnoses, whereas in fact the semen abnormalities are merely a reflection of underlying damage to spermatogenesis. There is currently great interest in the molecular biology of spermatogenesis and of spermatozoa and in the future it may be possible to identify defects and to repair these. It seems possible the measurement of germ cell-secreted proteins in semen may provide a much more accurate assessment of damage (Sharpe 1992) and this may enable better clinical correlation with specific defects and the development of new treatments. Alternatively it may become possible to treat defects in sperm after ejaculation and in association with assisted conception (see Chapter 20).

It is often difficult for the individual clinician to distinguish the spontaneous pregnancy rate (see Fig. 1.2) from treatment effect and this probably accounts for the continued popularity of empirical therapy. In uncontrolled studies the spontaneous pregnancy rate has often been interpreted as treatment effect. Also in some uncontrolled studies there is an apparent improvement in sperm analysis measurements but in controlled studies there is equal improvement in both the treatment group and the control group. The usual explanation for these apparently contradictory findings is regression to the mean. A brief explanation is as follows. Biological measurements are generally variable about a mean value. If a group of patients is selected on the basis of a single low measurement then it is likely that the next measurement in a series will be nearer or above the mean value and at first impression the random variation about the mean. Therefore, if men are selected for a treatment on the basis of a single low sperm
measurement then it is likely that the next measurement will better. This error is less likely if several baseline measurements are taken.

Another rationale for non-specific treatment is that there may be subgroups who respond to a particular treatment and that it is better to treat too many men rather than fail to treat someone who will benefit. Most clinicians have seen men who apparently improve with therapy and where the improvement is not easily explained by regression to the mean or spontaneous pregnancy. It remains possible that some stimulatory treatments work for selected patients. However, so far this cannot be demonstrated in a scientific way.

Finally, many clinicians find it easier to offer treatment for 3 to 6 months while the couple come to terms with their predicament and to prevent the couples trying too quickly expensive alternatives such as assisted conception. Other clinicians argue that empirical therapy should not be offered in the absence of proof of efficacy and that clinicians who believe in such therapies should be given better education opportunities! Also it is doubtful ethical practice to offer non-specific treatment even for a short time if the clinician knows that it does not work unless the couples are fully informed about the side effects, realistic benefits and costs of the treatment. However, to give such full information may prevent a useful placebo effect. At the time of writing this text empirical treatments are still widely used and some of the more commonly used empirical treatments are reviewed below.

**Antioestrogens: Clomiphene, Tamoxifen**

It is thought that oestrogens derived from androgens are an important element of feedback from the testis to the pituitary (Sherins and Loriaux 1973). Antioestrogens such as clomiphene and tamoxifen have been used to reduce the oestrogen stimulus to the pituitary in the hope that the resulting increased secretion of FSH and LH will cause increased intratesticular testosterone levels and improved spermatogenesis.

**Clomiphene**

Some results of treatment reported in the literature are shown in Table 19.1. Paulson (1977) tried to predict which patients were likely to respond; he found that those with depressed spermatogenesis and normal gonadotrophins were more likely to respond than those with abnormal testicular biopsies or elevated FSH levels. However, the results of a multicentre trial using a similar regimen to Paulson showed no group or subgroup to benefit from clomiphene when compared with vitamin C (Abel et al. 1982).

Clomiphene therapy may carry risks and until there is clear evidence of benefit it should not be prescribed other than during the course of a clinical investigation. Heller et al. (1969) pointed out that clomiphene might exert a direct damaging effect on the seminiferous tubules. Clomiphene has side effects of nausea and headaches and occasionally visual disturbance and possible cataract and if there is a family history of cataract it is best not used. The US Food and Drug Administration allow the use of clomiphene solely for the induction of ovulation in women. Similarly, in the UK clomiphene is licensed for use in women only.