Part one
Reproductive biology

1 Fertility and infertility

Since the 1950s, biologists have contributed greatly to advances in the reproductive sciences and medicine. The essence of this reproductive revolution has been its unifying character. Contributions from the disciplines of genetics, biochemistry, prenatal medicine, immunology, epidemiology, socioanthropology and ecological ethics have provided choices, accelerated social change and rewarded procreation through improved health. Despite these new opportunities, medical technology is not the only essential for solving many of our problems because health determinants, particularly reproductive health, are usually more dependent on increased political awareness and a rising socioeconomic level. The unhealthy aspects of reproduction are intimately connected through the stresses of severe crowding, poverty, inequality of resource distribution and political instability. Issues of human concern, including the consequences of unregulated fertility, infertility, infant/maternal mortality, intrauterine growth retardation, congenital abnormality, sexually-transmitted disease and environmental deterioration, are the central themes of this book and are integrated into the various chapters dealing with theories and principles of human reproductive function.

HEALTH DETERMINANTS

Reproductive health is predetermined by genetic endowment and by environment but it can be improved or undermined by individual behaviour, advanced by better socioeconomic conditions and changed by medical knowledge and services. Improved medical social services are essential to the raising of reproductive health but can only be effective if they facilitate the necessary changes in human behaviour. Health, as defined in the Constitution of the World Health Organization (WHO), is a state of

'complete physical, mental and social well-being not merely the absence of disease or infirmity', succinctly emphasizing the positive aspects of a realised potential. For reproductive health, three basic interconnected elements have to be satisfied. These are control of fertility, success in procreation and safety in their pursuit.

The regulation of reproductive potential requires the conscious separation of fertility from sexual pleasure and enjoyment of relationships. Men and women, since prehistoric times, have agreed that it is desirable that fertility be controlled. Not until the second half of the 20th century, however, has knowledge and technological development given humankind real control over fertility. Reproductive behaviour is an important health determinant which is essentially in individual hands. Planning of pregnancies to take place at optimal times and under optimal conditions makes a major contribution to better health for parents, children and society. Pregnancies too close, too early, too late and too many are high-risk behaviours that deny access to their potential for millions of people, who spend their lives uneducated, unhealthy and ill-housed. This loss of potential has serious physical, psychological, social and economic consequences. Numerous surveys show that many women, especially in developing countries, still have no control over their fertility. Aside from economic costs, unwanted fecundity transgresses on ecological issues. Species besides *Homo sapiens* have a right to exist, and *Homo sapiens* is a knowledgeable enough species to know that further environmental degradation is incompatible with survival.

A second aspect of reproductive health is the outcome. The birth of a healthy infant with good postnatal prospects, unencumbered by the effects of intrauterine deprivation, should be the norm. Socioeconomic improvement is a significant factor in alleviating high-risk pregnancies as it is the women and children under poverty who are the most vulnerable. In depressed societies, the status of women is also depressed and status raising factors, such as education, access to contraceptives, reasonable employment opportunities and equality under the law, are not generally available. For the millions of unplanned children, life is also predetermined by the poverty cycle which limits access to education and health services and denies them independence to withstand harmful traditional pressures. Traditionally, improved socioeconomic conditions have been linked to absolute economic growth. Significant improvements in reproductive health can, however, be achieved without corresponding economic growth because the absolute level of growth is less important than the manner in which the economic rewards are shared by members of the community

and whether the existing economic resources are managed sustainably. For instance, improving the status of women in a society will make a significant contribution to reproductive health within the same level of economic development and a healthier human resource will increase future economic productivity.

The last aspect of reproductive health relates to the reasonable expectation that engaging in sexual intercourse, fertility regulation, pregnancy and childbirth is not participating in a high-risk activity with adverse implications for partners or offspring. Safe reproduction is also a matter of basic human rights, especially those concerned with the health of the next generation. Too little is known about the etiology of congenital anomalies, but the majority of malformations at birth have a dual cause, comprising a genetic predisposition triggered by environmental teratogens. These include infectious diseases, therapeutic drugs, recreational drugs, psychological stress, radiation and environmental pollutants, most of which are human in origin. Humane communities generally judge that failure to provide life-preserving treatment to a newborn constitutes child neglect. Surely the failure to make adequate envionmental provisions during reproduction that would minimize the need for intervention at or after birth is equally culpable.

Reproduction is a very sensitive indicator of health status and can be impaired by a modest failure in physiological homeostasis. The United Nations' medium projection predicts that from our present 5 billion, the population will stabilize at between 8 and 14 billion some time in the next century. It is also predicted that more than 90% of the increase will occur in the poorest countries whose populations already overextend their available environmental resources. These projections are based on assumptions of fecundity and life expectancy which are largely guesswork and necessarily ignore the consequences of this enormous population growth on the human reproductive capacity. Paradoxically, one of the biological consequences of unregulated fertility is infertility (Chapter 13). Humans may not be exempt, as a survey by the US Office of Technology and Assessment found that the rate of infertility among women aged 20–24 years rose significantly from 3.6% in 1965 to 10.6% in 1982. In addition, the number of couples with primary infertility doubled, increasing from 500 000 in 1965 to 1 million in 1988. A British study suggested that subfertility was another problem that many couples confront, since 20–35% of pregnancies take more than 1 year to conceive. The legacy of unregulated population growth coupled with appalling environmental deterioration may be human infertility on a mass scale.

INFERTILITY: THE PRICE OF EXCESS FECUNDITY?

Pregnancy provides the best basis for assessing a couple's fecundity and a couple is considered infertile if no conception has been achieved after 12 months or more of unprotected coitus of average frequency. Infertility is hard to assess accurately, but several studies have reported that up to 15% of couples in developed countries are involuntarily infertile, with a much higher percentage in developing countries (30–40% of women in parts of tropical Africa). The main causes of infertility in developing countries are sexually-transmitted diseases (the main culprits are gonorrhoea and chlamydia) and repeated pregnancies causing secondary infertility due to poor hygiene at the time of childbirth, abortion or miscarriage. Infertility due to primary gonadal failure, such as permanent azoospermia or congenital absence of ovaries, can be described as sterility.

According to WHO figures, of the infertile couples (up to 80 million people worldwide) 30–40% have an exclusively male factor, 25% have factors in both male and female, 40% have a predominant female factor and in 2–15% no diagnosis can be made after a complete investigation. It has also been reported that in as many as 35% of couples the infertility may have multiple origins. Female infertility is age dependent and its rate increases from 30 years of age to the menopause. Since the 1970s, an increasing number of couples, mainly from western societies, have been seeking treatment for infertility. This may, of course, be due to an increased candour that the evolving reproductive technologies has encouraged, or it may reflect increased infertility resulting from, among other things, exposure to low concentrations of a range of toxins. Thousands of potential toxins are released continually into the environment, the great majority of which have never been studied for their effects on mammalian reproduction. The increasing number of women in the workforce has prompted many studies on the potential effects of occupational exposure to toxins on female reproduction. These studies have also been the impetus for similar investigations in men. Male occupational exposure to heat, noise, vibrations, radiation, microwaves, toxic chemicals such as lead, anaesthetics, pesticides and synthetic oestrogens may affect semen quality, fertility and libido. According to a US Office of Technology Assessment study, people working in agriculture, laboratories, oil, chemical and atomic industries, pulp and paper manufacturing, and textiles are most likely to be exposed to substances that adversely affect reproduction. Some scientists claim that an increase in several testicular abnormalities including cancer, undescended testicles and low sperm count could be linked to rising

levels of oestrogens in the environment. Environmental pollutants such as polychlorinated biphenyls (PCPs), some organochloride insecticides and detergents exhibit oestrogenic activity and may affect normal differentiation of male fetuses (Chapter 16). Lifestyle also modulates fertility; for example, an association between cigarette smoking and teratozoospermia (sperm morphology less than 50% normal) has been documented. Environmental factors may also increase impotency, which can be psychogenic, neurological or vascular in origin.

Male infertility

Men have almost always been assumed to be fertile so recognition of male infertility has been slow. Until the second half of the 20th century the blame for a couple's infertility was laid on the female partner. Now, scores of male infertility clinics exist around the world and the male reproductive science, andrology, has emerged and gained widespread acceptance. In fertile men, the sperm concentration varies between 60–80 million active sperm per ml of semen in an ejaculate volume of approximately 2.5–3.5 ml. The turning point between fertile and infertile sperm numbers is taken as 20 million active sperm per ml, but sperm density alone is insufficient to assess the quality of a semen sample. Other parameters such as sperm motility, viability and morphology are especially important. The least adequately assessed parameter of semen analysis is sperm morphology, which is, typically, examined on wet preparations or on smears of stained seminal fluid. Only morphological parameters, such as head size and shape, length and appearance of flagellum, presence or absence of multiple head or flagellae, are assessed because functional faults are beyond the limits of resolution of the light microscope. The transmission and scanning electron microscopes are useful tools in evaluating the ultramorphology of sperm as they permit a detailed assessment of structural integrity of subcellular components (Fig. 1.1). A more precise assessment of sperm motility can now be obtained with video micrographic, computer-assisted semen analysis systems that measure sperm velocity, progression, amplitude and frequency, and head movement. These measures permit a deeper evaluation of sperm function but such systems are expensive and are only available in sophisticated research centres.

Once sperm have arrived on site, other qualities needed for fertilization of oocytes, involving recognition, binding and penetration through the zona pellucida, and fusion with the vitelline membrane of the oocyte (Chapter 8), must be included. Diagnostic techniques and methods for

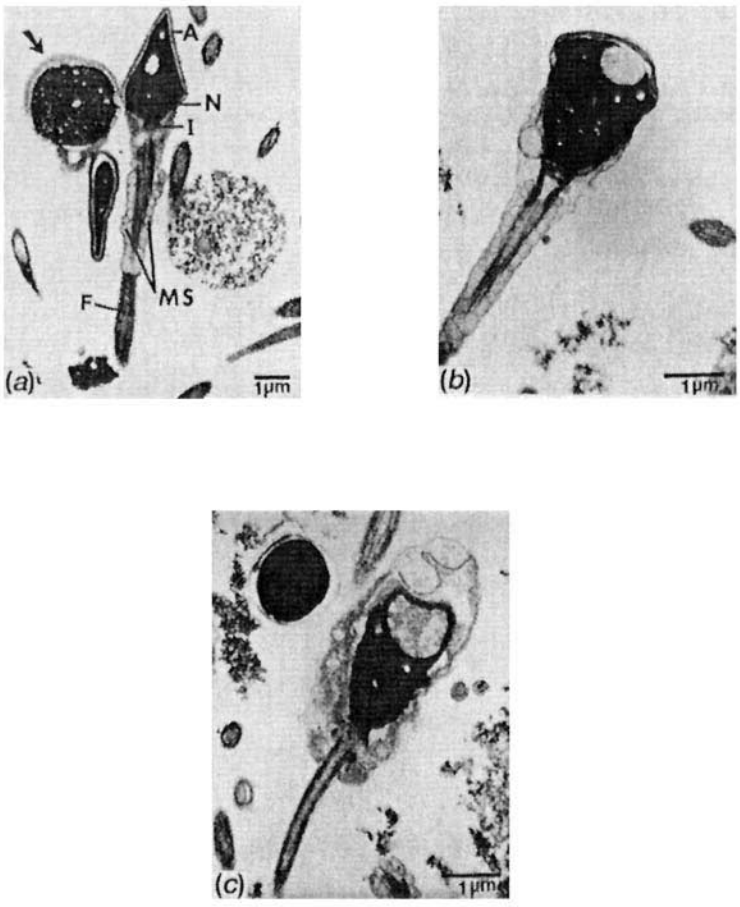

Fig. 1.1 Transmission electron micrograph showing normal and abnormal forms of human sperm. (*a*) A normal sperm showing the acrosome (A) covering the anterior part of the head or nucleus (N), implantation site (I), midpiece surrounded by the mitochrondrial sheath (MS) and the principal piece of flagellum (F). The round-headed abnormality (arrow) illustrated has a circular nucleus lacking an acrosome and has a detached flagellum. The round-headed syndrome is frequently described but represents less than 1% of sampled abnormal cells and occasionally can be found in 'normal' populations. (*b*) An abnormal sperm characterized by vacuolations in the nucleus and postacrosomal region with separation of the acrosomal membranes. (*c*) A grossly abnormal sperm characterized by extensive vacuolation of the nucleus, alteration of shape, incomplete formation of the acrosome and copious excess cytoplasm around the nucleus. I am indebted to R. A. Boadle, electron microscopist, Dept. of Anatomical Pathology, ICPMR Westmead Hospital, Sydney, for supplying this interesting photograph.

the *in vitro* assessment of the functional competence of human sperm include the sperm penetration assay (or the zona-free hamster oocyte test) and the hemizona assay. The sperm penetration assay employs hamster ova which have been separated from their surrounding zona pellucida before their incubation with sperm. Sperm capable of penetrating the vitelline membrane are considered capable of fertilization (the resulting 'humster' does not develop beyond the two-cell stage). The hemizona assay has been developed as a predictor of fertilization potential and uses matching halves of a human zona pellucida from a non-living oocyte to evaluate tight binding (as opposed to initial attachment). One half provides an internal control while the other half is observed for test binding. The assay index is derived from the percentage of bound sperm from a subfertile man over the percentage of bound sperm from a fertile control. Oocytes, fresh or frozen, come from surgically removed ovaries, post-mortem ovarian tissue and failures from IVF programmes. Sperm preparation protocols and reagents for the artificial enhancement of sperm function have also been developed. Sperm numbers and quality may be boosted in some men by large doses of vitamins B and/or C and frequent ejaculation.

Between 50 and 75% of all male infertility is asymptomatic and without demonstrable cause because, as already mentioned, functional defects place assessment of the sperm's integrity outside conventional semen analysis. Identified causes of infertility range from congenital defects to an inappropriate lifestyle (common modifiers of male fertility are further described in Chapters 5 and 8). The etiology of infertility can be classified under the following headings: testicular causes affecting spermatogenesis, post-testicular (ductal factors and sexual dysfunction), pretesticular (including endocrine disorders), immunological causes and bacterial, viral or parasitic urogenital infections. The frequency of known causes of infertility varies from country to country but common causes, in descending order of prevalence, include varicocele (dilation of the, commonly left, spermatic vein), testicular failure (idiopathic[1] oligospermia, generalized immotility or ineffective motility classed as asthenozoospermia and teratozoospermia), accessory gland infection, sperm autoimmunity, congenital abnormalities, systemic factors, sexual dysfunction and obstructive azoospermia. For example, a history of postpubertal mumps or sexually-transmitted disease, especially if not promptly treated, can result in seminiferous epithelial damage and ductal obstruction. Varicoceles occur in 10–20% of the general population but are present in approximately 40% of infertile men. Varicoceles result from inadequate venous drainage from the internal spermatic

[1] Of unknown cause.

vein. This results in varicosed areas and scrotal heating due to excessive venous pressure build-up. A real concern in this field is not so much infertility as subfertility and compromised reproductive capacity as this may be a source of congenital abnormalities of which 60% have no known cause and are thought to result from the interaction of genetic and environmental factors.

Female infertility

Fertility, often in the form of a goddess or phallic symbol, has been worshipped since ancient times because the 'barren woman' caused much concern. The etiologies of female infertility fall into similar categories to those listed for the male, although some kind of treatment for infertile women has always been available. Since the early 1960s, however, important breakthroughs, such as ovulation-inducing drugs and gynaecological microsurgery, have resulted in more women being successfully treated than their partners. Female infertility can be classified under the following broad categories: endocrine causes including anovulation and luteal phase defect, tubal occlusion, disorders of the cervix and uterus including malformation, abnormal growths (fibroids), endometriosis and hostile cervical mucus, immunological causes and infections. Both men and women can develop antisperm antibodies with some evidence that women infected with sexually-transmitted disease are more likely to develop antibodies against sperm because sperm come in contact with the immune system through genital lesions. Miscarriage is quite common in all pregnancies (15–20% of all human embryos die in the early stages of development, which serves as the mechanism for the selection of normal and near-normal embryos) but is significantly higher in communities with substandard hygiene, poor nutrition and a high rate of disease.

A major cause of infection in women is pelvic inflammatory disease (PID). It has been estimated that between 30–50% of all cases of female infertility and ectopic pregnancy are caused by PID-related tubal adhesions. Sexually-transmitted diseases underlie an estimated 75% of all cases of PID but infection after backstreet abortion and genital mutilation in African teenage girls at circumcision and/or infibulation also accounts for significant incidences of PID. The term PID was introduced because the condition is seldom confined to a single pelvic organ and is caused by an inflammatory infection in the upper genital tract. From the clinical point of view, the majority of women suffering from pelvic inflammatory infections may not even be aware of the original infection or recover

completely, but persistent morphological damage to various parts of the genital tract may result. In many cases the decreased or abolished reproductive capacity may not become apparent until years later. PID can involve one or both fallopian tubes (salpingitis), one or both ovaries (oophoritis), the uterus, and the peritoneum in the pelvis and abdominal wall. Many opportunistic infections may be introduced during coitus, especially if the immune system and the cervix (the natural barrier against the invasion of microorganisms) is compromised after miscarriage, abortion, cervical surgery, the presence of certain types of intrauterine contraceptive devices and primary infections, such as, *Neisseria gonorrhoea* and *Chlamydia trachomatis*. Since the 1980s chlamydial infection and gonorrhoea have increased in epidemic proportions with, globally, 200 million new cases of gonorrhoea reported to the WHO each year. Up to 20% of women thus infected will develop PID.

Complete or partial tubal occlusion may be diagnosed by hysterosalpingography which involves introducing radio-opaque dye through the uterus into the fallopian tubes under X-ray fluoroscopy visualization. When the dye moves into the fallopian tubes, occlusions or other abnormalities can be seen: if the fallopian tube is open, the dye fills the tube and spills into the abdominal cavity. If the hysterosalpingogram is abnormal, laparoscopy allows direct visualization of the pelvic organs through an endoscope. Complete or partial tubal blockage and adhesions can sometimes be corrected by microsurgery.

MEDICAL TECHNIQUES FOR ASSISTED REPRODUCTION

Efforts to overcome infertility by engaging in all manner of sexual practices and manipulations date back at least to Biblical times. Even to-day not all infertile couples seek infertility treatment with, in industrialized communities, an estimated 51% of couples with primary infertility and 22% with secondary infertility seeking treatment. The demand is, however, rising, probably as a result of a more conducive social milieu and familiarity with the available reproductive technologies. It may also be rising as a result of increased primary infertility (a failure to reach fertility), greater availability of services for secondary infertility (malfunction of the mature reproductive system) and a decreased number of infants available for adoption. Among infertile couples seeking medical treatment, 50% will achieve a viable pregnancy and 85–90% of these will be the result of conventional therapy. Ovulation induction, surgery and artificial insemina-