Iatrogenic injury is a feature of all medical practice but it is perhaps nowhere more accepted as an unavoidable consequence of therapy than in obstetric and neonatal medicine. Classical obstetric iatrogenic pathology has been with us since time immemorial, and despite the recognition of causal factors remains a not infrequent occurrence (Ennis and Vincent 1990; CESDI Fifth, Sixth, Seventh and Eighth Reports 1998–2001, www.cemach.org.uk).

The development of invasive antenatal investigation and treatment and the increasingly complex interventions in neonatology have resulted in the appearance of new types and patterns of pathology.

The role of the pathologist in the investigation of perinatal and neonatal death is central to the monitoring of iatrogenic pathology and brings with it considerable responsibilities in the light of potential medicolegal consequences and the need to recognize new problems. It is vital that the pathologist be well versed in the identification of iatrogenic lesions and record with great care unusual findings in cases where novel therapeutic modalities are being employed. Iatrogenic lesions may be of varying degrees of clinical significance. Many, perhaps the majority, are minor and accepted as a consequence of intervention, while others represent serious complications or medical mishaps or reflect poor clinical judgment. Perinatal autopsy examinations provide a vital opportunity to monitor any potential teratogenic effects of drug therapy. In addition, the ability to keep very ill babies alive in neonatal intensive care has resulted in the maturation or evolution of pathological processes in various organs, resulting in the development of new patterns of pathology that need to be recorded and explained.

It is clear that in order for pathologists to contribute effectively to the investigation of perinatal and neonatal deaths and to the understanding of iatrogenic pathology, they require full access to obstetric and neonatal records before they begin the examination. All medical devices, for example, cannulae, should be left in situ prior to the post-mortem examination. If these conditions are met, the pathologist can contribute markedly to the improvement in the quality of obstetric and neonatal care.

Maternal Medication During Pregnancy

The recognition that maternal drug therapy poses risks to the fetus at all stages of development has been hard won. The tragedy of thalidomide had a major influence on professional and public awareness, but continued vigilance is essential if further similar events are to be avoided. Current standards for testing of potential therapeutic agents for developmental toxicity has prevented any repetition of the thalidomide tragedy, and there have been no reported episodes of new unrecognized teratogens released into routine therapeutic use for more than two decades. Although the deleterious effects of some agents may appear idiosyncratic, the recognition and understanding of certain principles regarding the
harmful effects of drugs in general serve to guard against complacency. We now recognize that agents that bind to steroid hormone receptors, the aryl hydrocarbon receptor, or retinoid receptors are potential developmental toxins with likely teratogenic effects.

There is no effective maternal–fetal barrier against drugs ingested by pregnant women. Although for some substances the transplacental dispersion is concentration dependent, that is, dependent on the maternal dose ingested, it must be remembered that the placenta is a dynamic organ capable of facilitated and active transport by carrier molecules that may well increase placental transfer of a given substance to a greater extent than simple diffusion would permit. Thus it is possible that a drug or other molecule can achieve a higher concentration in the placenta and fetus than would normally be determined by the maternal serum concentration.

The harmful effects of drugs are substantially determined by the stage of development of the conceptus at the time of exposure. Thus developmental toxicity results from exposure in the embryonic period during which there is major organogenesis. This critical period extends from fertilization until approximately 60 days postconception, and the pattern of abnormality reflects the phase of organogenesis during the time of exposure. In the fetal period, that is 60 days postfertilization until birth, drugs may exert their deleterious influence by changes in the growth and functional development of organs. Drugs given late in pregnancy or during labor may also cause problems in the progress of labor or in the neonate postpartum. It should also be remembered that certain classes of drugs have long half-lives and can be teratogenic for months after the cessation of maternal therapy, for example, retinoic acid analogues.

Maternal ingestion of drugs that may affect the fetus can occur in the following circumstances:

1. Inadvertently, without the mother realizing she is pregnant
2. Taken in diagnosed pregnancy without consideration or knowledge of the risks involved
3. Therapeutic administration in the knowledge of pregnancy in the first trimester
4. Therapeutic administration in the knowledge of pregnancy in the second and third trimesters
5. Maternal administration of drugs intended to have a therapeutic effect on the fetus
6. Maternal therapies during labor
7. Maternal treatment postpartum in breastfeeding mothers

It has been calculated that approximately one third of all pregnancy women receive at least one course of drug therapy during pregnancy (Rubin et al. 1986). This apparently high rate, given the widespread understanding of the risks of drug ingestion in pregnancy, is a gross underestimation of the true incidence of fetal exposure in the first trimester to pharmacological agents as self-treatment by proprietary over-the-counter (OTC) medications, and continuation of prescribed therapy is frequent prior to the mother or her medical advisers knowing she is pregnant. This may be particularly critical given the fact that exposure is occurring during the phase of organogenesis, which is the period of greatest risk to the embryo.

As it is not possible to conduct clinical trials of the effects of drugs in humans in early pregnancy, we rely on the results of anecdotal occurrence or therapeutic disasters to identify teratogenic agents, and only a small number of drugs are definitely regarded as known teratogens if administered in the first trimester of pregnancy. It should also be noted that teratogenic effects may be dose dependent or may require the coadministration of other agents or synergistic influences if serious sequelae are to ensue. An additional complication in assessing the teratogenic effect of any agent is the background rate of congenital malformation in the community as a whole, some of which may be teratogenic in its own right, which is in the order of 1% to 2% of all pregnancies. An example of this difficulty is the thalidomide experience, in which it is now clear that some cases of limb reduction defect were in fact Roberts syndrome and not the result of thalidomide exposure in the mother. This has become apparent when children of apparent thalidomide victims are born with identical patterns of limb deficiency. A significant proportion, perhaps 10%, of congenital abnormalities result from environmental influences.