CHAPTER I

INTRODUCTION
INTRODUCTION

Schwalbe (1906) stated that malformation is a morphologic change which originates during foetal development and is therefore congenital, affecting one organ or more, the whole systems, or the entire body, and extends beyond the variability of the species. There was at first a tendency to overstress the hereditary component in the aetiology of the birth defects.

Stockard (1921) showed that environmental agents were capable of producing various types of malformations. He postulated that deformities produced in sea minnows by hypothermia or hypoxia were due to arrest of growth at specific times during development. Stockard was the first to call attention between the activity of a teratogen and the developmental stage at which it is applied to the embryo.

Though laboratory experience had demonstrated that a variety of agents could affect development in lower animals, it was believed that, in mammals, the placenta serves as an effective defensive barrier protecting the foetus from teratogenic insult. Consequently little experimental teratology was attempted in mammals until recently. The era of active investigation of mammalian
teratology began with the observations made by Hale (1933) in pigs, and later in rats by Warkany and Schraffenberger (1943 and 1944), that foetal malformations could be experimentally produced by maternal nutritional deficiencies. At about the same time Gregg (1941) reported the first clinical studies of the teratogenicity of rubella in man. An extensive literature of experimental teratology in mammals has since appeared.

Wilson (1959, 1961) put forward five generalizations related to experimental mammalian teratology:

1. The activity of a teratogenic agent depends upon the developmental stage at which it is applied to the embryo.

2. Because teratogens usually modify specific developmental events, individual teratogens tend to produce characteristic malformation patterns.

3. Both the maternal and foetal genotype modify the response to teratogenic agents.

4. Potent teratogenic agents may have little effect on the mother at the doses at which they produce malformed offspring.
5. The production of foetal malformations by teratogenic agents is associated with increased intrauterine mortality.

Later, in 1967, Kalter reviewed this subject and added the following principles:

1. A procedure that kills embryos and foetuses is not necessarily teratogenic.

2. Some teratogens may produce different types of malformations when administered at different times during pregnancy, whereas others are able to produce one type of defects regardless of when given.

3. The same or very similar defects may be produced by different teratogens.

Reproduction can be divided into four main stages; production of male and female germ cells (gametogenesis), division of the fertilized ovum and formation of the blastocyst lying free in the uterine cavity (blastogenesis), implantation followed by the development of the main layers and organs (embryogenesis) and growth and histological differentiation of the organs (foetogenesis). This last stage occupies the major period of prenatal life.
Lutwak-Mann (1964) gave thalidomide to male rabbits during various periods before mating and observed a few malformations in the offspring.

Kopf, Lorenz and Salewski (1964) treated the male and female rats for several months with thalidomide and observed that the resorption rate was higher than in controls, though histological examination of the gonads did not show any pathological changes.

Tuchmann-Duplessis (1965) stated that during the short pre-implantation period, exogenous agents do not in general produce malformations. The dividing ovum may be killed by marked physical or chemical injury, but when this is less severe, the damaged cells can be repaired or replaced so that development is resumed without impairment of organogenesis. The pre-implantation period corresponds to maximal fragility of the embryo, known as the embryotoxicity period.

Beck and Lloyd (1965) claimed that differentiation is a gradual process with no definite beginning and for this reason it would be wrong to make too much distinction between pre- and post-gastrulation stages. All what can be said with certainty is that there is
considerably less likelihood of induced malformation resulting from agents administered before rather than during or after gastrulation. They stated that once implantation of the ovum has ensured that the nutritional requirements for rapid growth and differentiation can be satisfied, gastrulation takes place. At this stage the embryo is highly susceptible to teratogenic agents, probably because a number of integrated processes are occurring simultaneously and interference with any or all of them could result in the production of a deformed embryo. The major malformations will result from agents which are active soon after implantation for at this stage the body axis and principal organ anlage are formed. Agents acting thereafter usually have less severe effects, often compatible with extrauterine life. During late embryonic and foetal stages susceptibility to teratogens is reduced as most of the important structures have been already formed. Nevertheless development is not complete and changes which are sensitive to external agents continue to take place. Hicks (1954) has described radiation malformations in rats and mice which can be induced well during the neonatal period and it is conceivable that a number
of teratogens might induce malformations at late stages of development by producing pathological degeneration.

Goertler (1964) working on the chick embryo observed that the critical teratogenic stage of each organ is correlated with the highest mitotic rate of the cells of that particular organ. Each organ might be thought of as having a susceptible period occurring early in the formation of its primordium, but it was found that these periods vary with the teratogenic agent employed because the latter will determine which facet of the developmental process is disturbed.

Fraser (1964) cited a two-hour nicotinamide inhibition by 6-amino-nicotinamide at 13 days of development as being maximally effective in preventing palate closure in the mouse (Goldstein, Pinsky and Fraser, 1963), whereas the period of maximum palatal sensitivity of X-rays lies between 10 and 12 days together with an earlier period of 8 days (Russell and Russell, 1954).

Another aspect is the relation of the time of treatment to the state of development of the materno-foetal exchange mechanisms. Beck and Lloyd (1965) stated that before implantation, the ovum is enclosed in the
zone pellucida which is relatively impermeable to substances in its immediate environment, and for this reason, most teratogenic agents are incapable of attacking it, while physical agents have been able to produce abnormalities when treatment is applied at this time. After nidation, pre-placental and placental mechanisms are constantly changing and the critical period of a teratogen may be due to its ability to interfere with the placental transport at one particular developmental stage. The same authors in 1956 suggested that the teratogenic action of trypan blue on the rat embryo is related to the form and function of the foetal membranes rather than to events referable to embryonic development.

Tuchmann-Duplessis and Mercier-Parot (1963a, 1963b, 1964a, 1964b) indicated that foetal death and foetal malformation may, at least in some cases, be separate during actions, and possibly contradict the belief that any drug that can kill foetuses will also deform them at lower doses (Woollam, 1962). Consequently there are two distinct types of toxic effects in teratology recorded by Robson, Poulson and Sullivan (1965):

1. Toxic effects leading to structural abnormalities, and
occurring during the phase of embryogenesis.

2. Toxic effects produced after embryogenesis are similar in nature to those which occur in adults but they have special significance in the foetus because they may lead to permanent defects or death.

Although most investigators are concerned with the first type, some observations are related to the second type as shown by the following examples:

a) The effect of chloroquine and of streptomycin which may cause deafness (Robinson and Cambon, 1964).

b) Antithyroid drugs which may cause cretinism (Robson, Poulson and Sullivan, 1965).

c) Indirect effects on the foetal pituitary, e.g. administration of cortisone to the mother which may cause foetal adrenal atrophy and death, and of testosterone which may lead to permanent sterility, (Robson, Poulson and Sullivan, 1965).

Robson, Poulson and Sullivan (1965) classified toxic effects on the embryo as follows:

1. The toxic effects may be produced directly on the foetus.

2. The drug metabolite may exert its action directly on the foetus.
3. The drug or its metabolite may have no direct effect on the foetus, and may even not reach the foetal tissues at all but it may produce foetal damage by or more one of the following mechanisms:

a) The toxic effect may be exerted on the maternal organs and the action so produced may affect the foetus secondarily.

b) The drug may produce its effect on the placenta which is essential for the nutrition of the foetus.

c) Interference with hormonal balance in the mother.

d) The drug may produce its effect primarily in males and the effect is then carried through the sperms to the conceptus (Lutwak-Mann, 1964).