INTRODUCTION

Epilepsy is a group of diverse disorders or diseases with a common central nervous system (CNS) manifestation, the occurrence of seizure. Seizure has been defined as "a state produced by an excessive discharge within the central nervous system" (Penfield and Jasper, 1954). The cause of epilepsy has been a subject of speculation for a long time. Some workers have emphasized the genetic factors (Lennox, 1951, 1960; Lennox and Jolly, 1954; Harvald, 1954; and Metrakos, 1960), while others have held the opposite view (Alstrom, 1950; Penfield and Paine, 1955; and Eisner et al., 1959, 1960).

Lennox (1951), in a study of 20,000 relatives of 4,231 epileptic patients found that the prevalence of epilepsy in their near relatives was significantly high, as compared with the general population. On the other hand, Alstrom (1950) in a study of 897 epileptics showed that the prevalence of seizure in the first degree-relatives was not significantly higher than that in the general population. Further,
Eisner et al. (1959, 1960) in a study of 660 epileptics and 470 control families, concluded that hereditary transmission of epilepsy could neither be demonstrated nor ruled out.

Various types of epilepsy can be classified according to their specific modes of inheritance, i.e., single gene or mendelian, polygenic, multifactorial and chromosomal (Anderson, 1978). Based on the findings in the families of epileptics, it has been postulated that in any individual, a number of variables must interact with the genotype in order to produce the final clinical and EEG phenotype with respect to epilepsy.

Neurochemistry, neurophysiology, seizure and anticonvulsants, all have one chemical compound of common interest, \( \gamma \)-aminobutyric acid (GABA). The compounds which inhibit the action of GABA, such as biculline, produce seizure, as do the compounds which inhibit GABA production (e.g., hydrazides). GABA is an important inhibitory substance in the cerebellum and there is evidence to suggest that stimulation of the cerebellum may be involved in the anticonvulsant
activity of phenytoin (Julien and Halpern, 1972). The anticonvulsant, dipropylacetic acid is known to elevate the GABA concentration in brain.

It is reported that cyclic adenosine 3'-5' monophosphate (cAMP) and cyclic guanosine 3',5' monophosphate (cGMP) are biologically important compounds of the central nervous system (CNS) (Bloom, 1975; Daly, 1977; and Phillis, 1970). It has been noted that seizures are associated with the altered (elevated) levels of these nucleotides (Ferrendelli and Kinscherf, 1977; Lust et al., 1976; and Stattin, 1971). The anticonvulsant drugs act by lowering the levels of one or both of these cyclic nucleotides.

Considering the elementary description of synaptic transmission, it can be assumed that three broad categories of events may determine the occurrence of a seizure: (1) an increase in excitatory synaptic influences; (2) a decrease in inhibitory synaptic influences, and (3) an alteration in normal neuronal membrane characteristics. Hence, the effective anticonvulsant drug should stabilize neuronal membranes, augment inhibitory processes or suppress excitation.
There is very little evidence of an advantage of polytherapy over monotherapy. Inspite of the chronic toxicity of drugs and their interactions, failure to evaluate individual drug, and exacerbation of seizures, polytherapy is widely and traditionally used for the treatment of different types of epilepsies.

A considerable amount of information regarding the effects of anticonvulsants on various biochemical mechanisms in neural tissue is now available. How some of the biochemical changes reportedly caused by these drugs are related to anticonvulsant effect is obscure. However, other drug-induced alterations in biochemical function appear potentially capable of anti-epileptic effects. These changes include:

1. alterations in energy production in neurons (necessary to maintain cell structure and the polarization of cell membranes, and to permit the synthesis of synaptic transmitter molecules),

2. alterations in ionic concentration gradients across cell membranes,
3. alterations in synaptic transmission,
4. alterations in folates, and
5. alterations in macromolecule synthesis.

Evidence of teratogenic effects of anticonvulsant drugs has been accumulating during the last decade. Anticonvulsant drugs like diphenylhydantoin (DPH) have been reported to be teratogenic in mice (Massay, 1966; Gibson et al., 1968; and Harvison et al., 1969). Some reports suggest that DPH may have similar action in man as well (Speidel and Meadow, 1972; and Monson et al., 1973). There is a general agreement that epileptic mothers are likely to have two to three times more malformed infants than those who never had a seizure (Meyer, 1973; Annegers et al., 1974; Janz, 1975; and Shapiro et al., 1976), suggesting the possibility that fetal damage may be due to epilepsy itself (Shapiro et al., 1976). However, the epileptic patients treated with anticonvulsant drugs show a higher incidence of anomalies in the offsprings than the untreated ones (South, 1972; Lowe, 1973; and Monson et al., 1973). The type of serious malformations most commonly seen
are cleft lip, cleft palate, congenital heart diseases, mental deficiency and microcephaly (Janz, 1975).

It has been suggested that seizures might have some role to play in the teratogenicity, and the severity of the seizure is considered as one of the risk factors for the teratogenicity. Studies have also been performed to find out the mutagenic effects of anticonvulsants on human lymphocyte chromosomes in vitro (Muniz et al., 1969; Grosse et al., 1972; Bishun et al., 1975; Alving et al., 1976, 1977; and others), and on rat bone-marrow cells in vivo (Alving et al., 1976, 1977). Adverse cytogenetic effects of anticonvulsants have been reported in these systems (Ayraud et al., 1968; Caratzali and Roman, 1969, 1971; and Brogger, 1970). Brogger (1970) observed chromosome and chromatid breaks in a boy treated with ethotoin. However, in some studies (Muniz et al., 1969; Bishun et al., 1975; Alving et al., 1977; and Esser et al., 1981) mutagenic effects of anticonvulsants could not be demonstrated. In most of the above mentioned studies only conventional techniques were used to assess the DNA damage, caused by the anticonvulsants.
The recently developed technique of studying "sister chromatid exchange" (SCE) has proved to be a very sensitive indicator of genetic damage caused by chemical and physical agents on eucaryotic chromosomes. The first direct observation of SCE in chromosomes was made by Taylor (1957) who found that if sister chromatids were made to differ from each other in respect of their radioactivity, they could be distinguished from one another in an autoradiogram. Due to its limited resolution and the use of tritium which itself causes SCE, this method had very limited utility. A new method to detect SCE, with better resolution and without the use of tritium label was developed by Latt (1973). This technique involved the exposure of cells to the thymidine analogue 5-bromodeoxyuridine (BUdR) or 5-iododeoxyuridine during two rounds of DNA replication. The subsequently observed metaphase chromosomes consist of one unifilarly substituted chromatid and another bifilarly substituted chromatid. Such substituted chromatids stain differentially with Giemsa, fluorescent compounds (Hoechst 33258, acridine orange) and a combination of fluorescent dyes with Giemsa (Perry
and Wolff, 1974; Wolff and Perry, 1974; and Korenberg and Freedlander, 1974). Latt (1974b) was the first to apply this method to human lymphocyte chromosomes which were treated with mitomycin C. A large number of SCEs was observed at concentrations too low to cause any alterations in chromosomal morphology.

Anticonvulsant drug, DPH, has been found to produce a linear increase in SCE frequency and decrease in mitotic index, with an increase in drug concentration (10, 15, 50 and 100 µg/ml) (Maurya and Goyle, 1981). At therapeutic dose (15 µg/ml), a significant increase in SCE frequency and significant decrease in mitotic index have been noted. However, no significant numerical or structural alteration in the chromosomes could be observed.

Keeping in view the basic information regarding epilepsy and the sensitivity of SCE technique in indicating the DNA damage, the present study has been undertaken on epileptic patients prior to, and after anticonvulsant therapy with the objective to determine the relationship between epilepsy (type, duration and seizure frequency) and anticonvulsants (duration of treatment) to genetic damage (SCE frequency and mitotic index).