DISCUSSION

Mitotic Index

Several factors, both internal as well as external are known to exert considerable influence on the course of nuclear division and chromosomal structure. Metabolic conditions, water content, temperature, irradiation and even administration of chemicals can alter the progression of a cell-cycle and in turn affect mitosis (Sybenga, 1972). Anticonvulsant drugs, which have been reported to be teratogenic and mutagenic, are found to show an inhibiting effect on mitotic index in in vitro studies (Maurya and Goyle, 1981).

Present study with epileptic patients reveals that mitotic index varies in response to anticonvulsant therapy according to age, sex, duration of epilepsy, age of onset of epilepsy, duration of therapy and seizure status of the patient.

Mitotic Index in Relation to Age: In the epileptic patients not on anticonvulsant therapy, the incidence of congenital malformations has been reported by several workers. The rate of malformations was noticed to be 10% (Meyer, 1973), 3% (Koppe et al., 1973), 2.7% (Lowe, 1973).
and 1.8% (Annegers, 1974). Shapiro et al. (1976), based on their findings raised the possibility that fetal damage may be due to epilepsy itself. Friis (1979) in accordance with the observations of Shapiro et al. (1976) also suggested that "Epilepsy per se may be a factor in the production of facial cleft" in the offsprings of epileptics.

Present study does not indicate any significant linear correlation in mitotic index value with increase in age both, in control and epileptics (treated and untreated) cases. Both, untreated and treated cases show a significant drop ($P < 0.001$) in mitotic index compared with controls for the respective age groups. But, between untreated and treated cases, a significant difference in mitotic index is observed only in the (21-30 yr) age group.

Age related variations in the metabolism of anti-convulsant drugs have been reported by many workers. However, the results are inconclusive. Seidl et al. (1966) found that patients over the age of 50 years developed drug reactions more commonly than younger patients. On the other hand, Ogilvie and Ruedy (1967) did not find any age related predisposition of drugs.
Hurwitz (1969) however, found significantly more adverse reactions in the patients of 60 years of age and over. O'Malley et al. (1971) showed that the half-life of antipyrene was significantly longer in healthy geriatric patients (mean age 77.6 years) than in the younger controls (mean age 26 years).

Svensmark and Buchthal (1964) found that children metabolized phenytoin at a faster rate than adults. Jalling et al. (1970), and Dawson and Jamieson (1971) both confirmed that young children required a larger dose of phenytoin/kg of body weight in order to achieve the therapeutic concentrations. Recently, Houghton et al. (1975) reported that though their results show a positive correlation between serum phenytoin concentration with age and negatively correlated with body weight and height, the magnitude of the multiple correlation coefficients indicate that these factors account for only a small part of the variations between patients. It was suggested by them that other factors, such as genetic differences and the effect of saturation kinetics are more important in determining steady-state concentration of the drugs.
Mitotic Index in Relation to Sex: The possibility of an epileptic father playing a role in the production of congenital malformations in the offsprings has been suggested by Annegers et al. (1974). They observed malformations in 8 out of 200 infants (40/1000). Shapiro et al. (1976) suggested that paternal epilepsy may increase the risk of birth defects in the offspring although, they found no evidence that antenatal exposure to phenytoin further increased the malformation risk. On the other hand, Monsoon et al. (1976) reported that paternal epilepsy is less involved with congenital malformations in the offsprings as compared with maternal epilepsy.

Friis (1979) noted in his study that the prevalence of epilepsy among the parents of facial cleft children was 2.3%, with a paternal and maternal prevalence of 1.8% and 2.8%, respectively. However, the difference was insignificant. Present study shows a significantly low mitotic index in untreated and treated male epileptic patients compared with respective female. Treated female epileptics show a significant fall in mitotic index compared with untreated, whereas in male cases this difference is insignificant. The results of
Herha and Obe (1977) show that with different drug combinations, the frequency of aberrations vary between male and female epileptics. He observed in a group of 10 epileptics on carbamazepine and diphenylhydantoin, 3 dicentric chromosomes/600 mitosis in female (3 cases) while, 4 dicentric chromosomes/1400 mitosis in 7 male cases. However, in 6 patients on carbamazepine and primidone, no chromosomal aberrations were noticed in 2 female cases, whereas, in four male cases, six chromosomal aberrations were noticed/800 mitosis.

Possible damage to genetic material by anti-epileptic medication before conception as a cause of congenital anomalies was studied by Meyer (1973) in 270 children of 142 epileptic patients. Only 3% children of untreated fathers had congenital anomalies, whereas 15% children of treated fathers had defects, and this difference was significant. However, he suggested that this higher appearance of anomalies in the children of fathers treated before conception with anti-epileptic drugs does not establish a mutagenic effect.
Shapiro et al. (1976) reported that total malformation rate in 305 children born to treated epileptic mothers was 10.5% as against 6.4% in the controls (neither parent epileptic). When the father had epilepsy the malformation-rate in their children (396) was intermediate (i.e., 8.3%). This study suggests that the anticonvulsant therapy affects more the children of epileptic mother compared to father. An incidence of malformations in the offsprings of treated epileptics has also been reported but the results of various workers do not arrive at the same conclusion, i.e., anticonvulsant treatment of epileptics increases the risk of congenital malformations compared to either, nonepileptics or epileptics without treatment. Janz and Fuchs (1964) reported that the total incidence of malformations in the treated female epileptics (22/1000 births) was not considerably different from that found in the population at large (20/1000). The results of Watson and Spellacy (1971) support the conclusion of Janz and Fuchs (1964) that there was no increased risk in the treated female epileptics. Present study, however, shows that in both, male and female untreated epileptics the mitotic index is significantly low compared with
controls. With anticonvulsant therapy, mitotic index drops significantly only in female patients compared with untreated. Elshove and van Eck (1971) reported 8 times more frequent malformations in epileptic mothers taking anticonvulsant drugs compared with nonepileptics. South (1972) reported a 70-fold increase in the incidence of cleft-lip in children of women with epilepsy taking anticonvulsant drugs compared with the general population. Speidal and Meadow (1972) observed that the risk in women taking anticonvulsant drugs is 2-3 times higher compared to normal population. Koppe et al. (1973) reported 8.8% and 3% incidence of malformations in the offsprings of epileptics taking anticonvulsant drugs and without treatment, respectively. However, the difference was not significant. Monson et al. (1973) concluded from his study that the probability of having a malformed child appears to be 2-3 times greater in epileptic women who received diphenylhydantoin early in pregnancy than nonepileptic women. Lowe et al. (1973) also found a significant difference in the frequency of malformations between treated (6.7%) and untreated patients (2.7%). However, Annegers (1974) did not notice any significant difference in the
incidence of malformations between treated and untreated patients.

A sex related difference in the metabolism of drugs has also been reported by various workers. Drugs like morphine, methadone (Axelord, 1956), Hexobarbitone (Quinn et al., 1958) and pentobarbitone (Kuntzman et al., 1966) have been found to be metabolized faster in male rats compared with the females. Vessel and Page (1968a, b) found that the metabolism of antipyrene and phenylbutazone is slightly lower in male rats. Hurwitz (1969) reported a higher incidence of adverse drug reactions in women compared with men. Present study shows that with anticonvulsant polytherapy, the mitotic index is significantly low only in females compared with untreated patients. Quinn et al. (1971) however, reported that the serum half-life of antipyrene is longer in men than in women, and suggested that men seem to be slower metabolizers of drugs than women and it might be expected that men would be more sensitive to drugs. On the other hand, Travers et al. (1972) reported that women had a lower serum phenytoin concentration than men treated with the identical dose/kg of body weight but, the difference was not significant. Similarly,
Houghton et al. (1975) noticed no appreciable difference in mean concentration of the drug in men and women treated with the same dose of phenytoin. However, when adjustment was made for the difference in height and weight between the two sexes, it was found that in general, women had lower concentration but, the difference was not significant.

In general, these studies suggest that the metabolism of the drugs not only differs in the two sexes but also for the different drugs the response varies.

Mitotic Index in Relation to Age/Sex: In the offsprings of untreated mothers, malformations have been reported by Meyer (1973), Koppe et al. (1973), Lowe (1973) and Annegers (1974). The possibility of epileptic father playing a role in the production of malformed children has also been suggested by Annegers et al. (1974), Shapiro et al. (1976) and Monson et al. (1976). Friis et al. (1979) in accordance of the possibility raised by Shapiro et al. (1976), also suggested that epilepsy itself may be a factor for the incidence of malformations noted in the offsprings of epileptics. In the present study, male cases both untreated and treated show significantly low mitotic index compared with female.
Furlanut et al. (1978) reported that in male epileptics there is no correlation between dose, serum level and age of the patients for two anticonvulsant drugs, diphenylhydantoin and phenobarbital. In the present study, the patients were on poly-anticonvulsant therapy which may again increase the possibility of interindividual variations in response to therapy. Sex based differences in the metabolism of drugs have also been reported. In rat, metabolism is often faster in male animals (Quinn et al., 1958; Kuntzman et al., 1966). In humans, the serum half-life of antipyrine is longer in men than in women of a comparable age (O'Malley et al., 1971). Houghton et al. (1975) reported that in general women had lower concentration of phenytoin compared with male, treated with the same dose. It seems that the differences in metabolism of anticonvulsant drugs in the male and female epileptics may possibly be responsible for the observed variation in the mitotic index between male and female epileptics in the present study. Male untreated cases show a significant increase in mitotic index with age. It is significantly low in both the sexes (untreated and treated) compared with control. In 10-20 years age range, mitotic index in
male treated cases shows a significant increase and a fall in female, compared with respective untreated cases.

**Mitotic Index in Relation to Duration of Epilepsy:** In the present study, mitotic index is significantly low in untreated epileptics, but significantly high in treated cases of 3-5 years duration of epilepsy compared with other durations. However, no specific trend between mitotic index and duration of epilepsy is observed both in untreated and treated patients. In the same way, age of onset of epilepsy also does not show any correlation with mitotic index, both in untreated and treated patients. It has been reported that the metabolism of anticonvulsant drugs depends upon various factors like age (Svensmark and Buchthal, 1964; Hurwitz, 1969; Jalling et al., 1970; Dawson and Jamieson, 1971; O'Malley, 1971), sex (Kuntzman et al., 1966; O'Malley et al., 1971), body weight and height (Houghton et al., 1975).

**Mitotic Index in Relation to Seizure Status:** Patients (untreated and treated) suffering from "minor" or "major attack" show a significant fall in mitotic index compared with the control. Those on polytherapy, experiencing
no attack also have a significantly low mitotic index compared with normal (Table 7). Reports on the seizure inducing the fetal damage are conflicting. Janz and Fuchs (1964a,b) did not find any evidence for the possibility that seizures produce either anoxemic or traumatically induced complications of the pregnancy or damage to the fetus. They reported that healthy infants were born even to mothers who suffered from a malignant course of epilepsy and status epilepticus. Similar reports also came from Maroni and Markoff (1969). On the other hand, Meadow (1970) reported that about a quarter of the mothers of 32 children with lip and/or palate cleft had a fit during the first 3 months of their pregnancies. Speidal and Meadow (1972) however, reported that there was no significant difference in the frequency of convulsions between mothers with malformed baby or those with normal baby. It was suggested that the stage in the fetal development when fits occur may be more important than the frequency. They have also suggested that etiology of the increased incidence of congenital anomalies may be a mixture of hereditary factors, seizures and their treatment. It was further pointed out that it is possible that an epileptic woman may be limited in her
choice of husband with the consequence that their off-
springs have a poor genetic background. Starreveld-
Zimmerman et al. (1975) reported that the tonic-clonic
seizures of the mothers seemed to occur appreciably more
often in the case of malformed babies compared with the
normal.

Elshove (1969) found a familial occurrence of
congenital anomalies in 4 cases among 10 women with
epilepsy who gave birth to malformed children. Starre-
veld-Zimmerman et al. (1975) also reported that 6 of 18
mothers had relatives with congenital abnormalities. It
is evident from these studies that the higher incidence
of congenital malformations in the offsprings of epile-
ptics may not be caused by seizure only; hereditary
factors, genetic background of the patient and treatment
also are important.

Duration of Therapy and Mitotic Index: Direct correla-
tion between duration of therapy (0-5 to 16-20 years) and
mitotic index has not been observed (Table 8). Herha
and Obe (1976) reported a significantly high incidence
of chromosomal aberrations in the epileptic patients
taking carbamazepine (1-8 years) and diphenylhydantoin
(2-10 years). On the other hand, Knuutila et al. (1977) did not observe significant increase in the frequency of chromosomal aberrations in epileptic patients treated with phenytoin for a duration of 7 months to 6 years. Similarly, Kotlarek and Faust (1978) also did not observe significantly high chromosomal aberrations in the epileptic patients on dipropylacetate monotherapy for 6 months to 4 years. More recently, Esser et al. (1981) also reported no elevation in chromosomal aberrations in the epileptic patients on either phenytoin (1-2 years) or primidone (1-2 years).

Mitotic Index and Drug Response: The results presented in Table 9 show that cases with good response have the highest mitotic index. In the patients with poor, fair and excellent response the mitotic index is not statistically significant from each other (P > 0.05).

Numerical and Structural Chromosomal Alterations in Epileptic Patients

In the present study, neither numerical, nor structural chromosomal changes have been observed in epileptics (treated and untreated). Earlier studies by Muniz et al. (1969) reported no structural anomalies.
in the chromosomes of lymphocytes of 7 patients treated with diphenylhydantoin at the therapeutic level (1-20 μg/ml). Caratazali and Roman (1971) reported chromosomal abnormalities in mice treated with phenytoin or primidone. Grosse et al. (1972) also observed a significantly high number of chromosomal breaks in 32 epileptic mothers on anticonvulsant therapy and in their children. Bartsch (1975) did not observe an elevation of chromosomal aberrations in the lymphocytes from patients receiving anticonvulsant medication (diphenylhydantoin and primidone). Herha and Obe (1976, 1977) reported that anticonvulsant treatment of epileptic patients leads to an elevation of exchange-type chromosomal abnormalities. Studies by Alving et al. (1977) on adult epileptic patients (4 females + 6 male, age range 19-49 years) showed that phenytoin (20 mg/litre) does not significantly increase chromosomal aberrations compared with the controls. Knuutila et al. (1977) in a study on the bone marrow cells of 22 epileptic patients (12 female + 10 male, age range 4-47 years) reported that therapeutic dosage of phenytoin does not cause chromosomal abnormalities. Kotlarek and Faust (1978) reported in a group of 10 patients (children age range
that a daily dose of 25-40 mg/kg body weight does not cause a significant increase in chromosomal aberrations compared with the control. Recently, Esser et al. (1981) also did not notice any significant increase of chromosomal aberrations in a group of 20 epileptic patients (children, 10 male + 10 female, age range 3-15 years) who were on monotherapy either with primidone (1.9 - 13.5 μg/ml) or phenytoin (4.8 - 26.4 μg/ml).

Folate deficiency, one possible side effect of anticonvulsant drugs (Latham et al., 1973; Reynolds, 1973; Janz, 1975), could explain the cytogenetic abnormalities that some of the investigators have attributed to phenytoin. There is now good evidence that folate deficiency may cause cytogenetic defects (Neath, 1966; Lawler, 1972). Meadow (1968, 1970) also suggested that malformations could be related to drug induced lack of folic acid. However, Marsh and Frazer (1973) suggested that diphenylhydantoin does not reduce the level of folic acid, but it disturbs the conversion of folic acid to metabolically active derivatives. Roman and Caratazali (1971) suggested that the
chromosomal abnormalities induced by anticonvulsant drugs are caused either by the inhibition of folic acid synthesis, which is one of the precursors of inosine synthesis, playing a fundamental role in purine biosynthesis, or by the inhibition of chromosomal matrix, thus interfering with the normal development of mitosis.
SCE Frequency

The assessment of sister chromatid exchange (SCE) by employing BUdR-differential staining technique is becoming an important tool for evaluating the chromosomal damage. An increase in the SCE frequency with mutagenic and carcinogenic chemicals has been reported at concentrations which are non-cytotoxic and non-clastogenic (Perry and Evans, 1975). According to Latt (1981) SCE is directly related to chromosome breaks but the relative frequencies of SCEs and aberrations exhibit no direct correspondence. It was suggested by Rewell (1959) and Heddie et al. (1969) that when an ionizing particle traverses the chromosome, it produces the primary event which is not a break but, an initiation of an exchange between the two chromatids and, if it is incomplete, chromatid break occurs. However, it is not known that an increase in SCE frequency represents damage which will ultimately lead to lethality or, by contrast represents repair which permits cell survival (Craig-Holmes and Shaw, 1977). Since chromosomal aberrations are associated with cell lethality, but do not correlate with SCE, Wolff et al. (1977) concluded that SCEs may
be "more representative of events compatible with cell survival, including mutagenicity".

**Effect of age on SCE frequency:** In control cases, although, a significantly high SCE frequency has been observed in 31-50 years age group compared with 21-30 \( (P < 0.02) \), it is insignificant for both the groups compared with 10-20 \( (P > 0.05) \) (Table 10). de Aree (1981) observed that the difference in the SCE frequency between 0-10, 30-40 and 60-70 years age groups of normal cases is insignificant. Similarly, Duker (1981) found no significant difference in the SCE frequency of newborn children and adult, normal cases.

In untreated epileptic cases, studies have not been reported on the SCE frequency in relation to age. Present study shows, it is significantly high in all the age groups compared with the controls. Amongst pretherapy cases, it is significantly high for 10-20 years age group compared with only 31-50 and insignificant to 21-30 \( (P > 0.05) \).

Incidence of congenital malformations has been reported to be 10% (Meyer, 1973), 3% (Koppe et al., 1973), 2.7% (Lowe, 1973) and 2% (Annegers, 1974), in the offsprings of epileptic patients not taking anticonvulsant drugs.
Shapiro et al. (1976) and Friss (1979) suggested that epilepsy itself may be a factor responsible for the congenital malformations in the offsprings of epileptic patients.

The present study indicates that SCE frequency is significantly high in epileptic patients compared with the normal population. However, Janz and Fuchs (1964) observed no significant congenital abnormalities among the 133 children of epileptic mothers not on anti-convulsant therapy. Similar observations were made by South (1972) and Speidal and Meadow (1972). Janz (1975) suggested that congenital malformations in the offsprings of epileptic patients could be produced by mutagenic (genetic damage) or teratogenic effects.

In epileptic patients on therapy SCE frequency is significantly low for all the age groups compared with the untreated. However, compared with control it is significantly high (Table 10). Hunke and Carpenter (1978) did not find any significant increase in SCE frequency in epileptic patients on DPH therapy compared with control. On the other hand, in vitro study by Hunke and Carpenter (1978) showed a significant increase in SCE frequency in
lymphocytes exposed to DPH. Habeltank et al. (1982) reported a significantly high SCE frequency in DPH-treated epileptic patients (6-16 yrs) compared with the control.

SCE frequency does not show any correlation with age in epileptics on anticonvulsant therapy (Table 10). It is significantly high in 21-30 years age group compared to both 10-20 and 31-50 (which are not statistically significant from each other (P > 0.05). Various workers have reported age related variations in the metabolism of drugs. Svensmark and Buchthal (1964) reported that the rate of phenytoin metabolism is faster in children compared with the adults and related this with the higher basal metabolic rate per kg found in the children. Seidl et al. (1966) found that patients over the age of 50 years developed drug reactions more commonly than younger patients. However, Ogilvie and Ruedy (1967) noticed no age related predisposition of the drugs. Hurwitz (1969) observed significantly higher rate of adverse reactions in the patients over 59 years of age. Jalling et al. (1970) and Dawson and Jamieson (1971) reported that children required a larger dose of phenytoin/kg of body weight in order to achieve the therapeutic concentrations. Kutt
(1971) noticed that the actual blood and tissue concentration of DPH depends more on rates of DPH metabolism in each patient. O'Malley et al. (1971) showed that the half-life of antipyrene was significantly longer in healthy geriatric patients (mean age 77.6 years) compared with the younger controls (26 years). Lascelles et al. (1970) reported that adult patients on a standard dose of phenytoin have a wide scatter of serum level, with over half outside the therapeutic level of 10-20 mg/ml. However, Houghton et al. (1975) suggested that factors like age, weight and height account for only a small part of the variations between patients. Recently, Furlanut et al. (1978) also reported no correlation between age and serum concentration of either DPH or phenobarbital.

It is evident from these studies that age related variations in the metabolism of drugs constitute only a small part. Instead, as suggested by Houghton et al. (1975), genetic factors and the saturation kinetics of the drugs may be more important. Probably, lack of linear relationship between age and SCE frequency in the present study is due to genetic differences in
the metabolism of anticonvulsant drugs or, variation in the saturation kinetics of drugs, from patient to patient.

**SCE frequency in relation to Sex:** SCE frequency between male and female control cases is statistically insignificant (P > 0.05). de Aree (1981) also observed that sexes do not differ significantly in their mean number of SCE/cell. Similarly, Duiker (1981) did not find any significant difference in the SCE frequency between male and female adults. However, male epileptics (untreated and treated) show a significantly high SCE frequency compared with the respective female (P < 0.001).

In both, male and female (untreated and treated) epileptics, SCE frequency is significantly high compared with the respective controls. Janz and Fuchs (1964), and Watson and Spellacy (1971) observed that there was no increased risk in the treated mothers as compared with the normal population. On the other hand, the incidence of congenital malformations in the offsprings of epileptic mothers is reported to be higher compared with the normal population. It is 8 times (Elshove and van Eck, 1971), 70-folds (South, 1972) and 2-3 times (Speidal and Meadow, 1972; Lowe, 1973; and Monson et al., 1973), more
in the offsprings of epileptic mothers taking anticonvulsant drugs compared with the general population.

There are conflicting reports with regard to the incidence of malformations in the offsprings of an epileptic father or mother. Annegers et al. (1974) reported increased malformation rate among 200 children of epileptic father. On the other hand, according to Shapiro et al. (1976), the malformation rate in the offsprings of epileptic father was 8.3% as against 10.5% and 6.4%, in the epileptic mothers and general population, respectively. Similarly, Monson et al. (1976) reported that paternal epilepsy is less involved with congenital malformations. However, Friis (1979) observed that the paternal and maternal prevalence of epilepsy was 1.8% and 2.8%, respectively, among the parents of facial cleft children but the difference was insignificant.

Lowe (1973) reported a significantly high frequency of malformations in offsprings of treated (6.7%) compared with untreated epileptic mothers. Similarly, Koppe et al. (1973) observed 8.8% and 3% incidence of malformations in the offsprings of these two groups respectively. On the other hand, Annegers (1974) and
Shapiro et al. (1976) did not find any significant difference in the malformation rate in the offsprings of treated and untreated patients. A comparison of SCE frequency between untreated and treated both, male and female epileptics (Table 11) shows that it is significantly higher in the untreated group.

The variation in SCE frequency between male and female treated epileptic patients may be due to differences in the metabolism of drugs between the two sexes. Many drugs like, morphine, methadone and mepridine (Axelord, 1956), hexobarbitons (Quinn et al., 1958) and phenobarbitalone (Kuntzman, 1966), are metabolized at a faster rate in male rats compared with the female. On the other hand, Vessel and Page (1968a, b) reported slightly lower rate of metabolism for antipyrenes and phenylbutazons, in the male rats. Hurwitz (1969) reported a higher incidence of adverse drug reactions in women compared with men. Quinn (1971) reported longer half-life of antipyrene in men and suggested that men would be more sensitive to drugs. Travers et al. (1972) and Houghton et al. (1975) reported that in general, women had lower concentration of anticonvulsant drugs than men treated with an identical dose/kg body weight.
SCE frequency in relation to Age/Sex: Normal male subjects show an increase in SCE frequency with age (21-30 years to 31-50). Considering SCE as a sensitive indicator of mutagenicity, it seems the risk of mutagenicity increases with age in healthy persons. As suggested by Needermuller (1978), younger cases are less exposed to environmental factors like radiations and have better DNA-repair capacity than older, these may be the possible reasons for low SCE frequency in the younger age group. de Aree (1981) reported a higher SCE frequency in 31-40 years age group compared with 0-10 and 60-70, and suggested the possible influence of the general hormonal status of the individuals as cause for this variation among various age groups.

Male epileptics (untreated) show a significant fall in SCE frequency with increase in age. As compared with the respective controls, both male and female epileptic patients show a significantly high SCE frequency in the various age groups studied.

In treated cases (both male and female), the SCE frequency is significantly low compared with untreated but high as compared with the controls of respective age
range. These results show that therapy does not increase the mutagenic risk compared with the pretherapy cases. Earlier reports by Elshove and van Eck (1971), South (1972), Speidal and Meadow (1973) and Monson et al. (1973) show that the risk of congenital malformations is higher in the treated epileptics compared with the normal population. Further, Lowe (1973) and Koppe et al. (1973) reported a higher incidence of congenital malformations in the offsprings of treated epileptic patients compared with the untreated.

Duration of epilepsy and SCE frequency: Fedrick (1973) reported that there is no relationship between duration of epilepsy and in the development of a malformed baby. The present study also shows no direct relationship between duration of epilepsy and SCE frequency in both treated and untreated epileptics. Treated cases show significantly low SCE frequency in 3-5 years duration compared with 1-2 and 6-10. It appears from these results that the risk of genetic damage is significantly high in the epileptic patients in 3-5 years duration group, but with therapy, in this group the risk is significantly low. Results also show that there is no correlation between SCE frequency and age of onset of epilepsy.
Seizure status and SCE frequency: SCE frequency shows an increase with seizure severity in the epileptic patients, both, untreated and treated. Treated cases with no attack also show a significantly high SCE frequency compared with the control. The SCE frequency in treated cases with minor attack is significantly low compared with the untreated. However, this difference is insignificant in cases with major attack.

Janz and Fuchs (1964a,b), and Maroni and Markoff (1969) did not find any evidence for the possibility that seizures produce damage to the fetus. On the other hand, Meadow (1970) observed that about 25% mothers of 32 children with cleft lip or palate had a fit during the first trimester of their pregnancies. Fedrick (1973) reported that the woman whose epilepsy is so well controlled that she experiences no attack, still has a high risk to get a malformed baby. Starreveld-Zimmerman (1975) reported that the occurrence of tonic-clonic seizures was appreciably more in mother of malformed babies compared with the normal. Present study also shows that epileptic cases with no attack have significantly high SCE frequency compared with the control.
Meadow (1968, 1970) reported that teratogenic drugs, aminopterin and methotrexate are folic acid antagonists, just as are hydantoins and barbiturates. He suggested that malformations could be related to drug induced lack of folic acid. Heath (1966) and Lawler et al. (1972) reported that the folic acid deficiency may cause cytogenetic defects. Kernis et al. (1973) observed that animals which are not susceptible to DPH-induced anomalies, such as the rats, do not have a reduced folic-acid level. Present study indicates an increase in the risk of genetic damage (high SCE frequency) in treated epileptics compared with the controls.

**SCE frequency and duration of therapy:** Present results indicate a significant increase in SCE frequency up to ten years of duration of therapy. Subsequently, no correlation was observed. Earlier study by Habedank et al. (1982) showed no correlation between the SCE frequency and duration of therapy in the epileptic children on long term phenytoin therapy.

The metabolism of anticonvulsant drugs has been reported to depend upon various factors like age, sex, genetic differences and saturation kinetics of these
drugs. Svensmark and Buchthal (1964) have reported that children metabolized phenytoin at a faster rate compared with the adults. Drugs like, methadone, morphine and meperidine (Axelord, 1956), hexobarbitons (Quinn et al., 1958) and phenobarbitone (Kuntzman et al., 1966) are metabolized at a faster rate in male rats compared with the female. Hurwitz (1969) observed an increased rate of adverse drug reactions in the patients over 59 years of age. Koch-Weser (1972) reported that completeness of absorption of the drugs was one of the most important factors in determining the plasma level. This depends upon various factors like solubility, disintegration and dissolution rates of solid drugs, particle size, pH of the gastrointestinal fluids, pka of the drugs, and amount of the food present. Mawar et al. (1974) suggested that the dose at which saturation occurs differs considerably from patient to patient.

Response to therapy in relation to SCE frequency:
The SCE frequency is significantly high in cases with poor response to therapy. It decreases significantly and linearly in the patients with fair, good and
excellent response. Keeping in view that SCE is a sensitive indicator of genetic damage (Perry and Evans, 1975), these results show that the risk of genetic-damage, i.e., mutagenicity is linearly correlated with response to therapy. However, there are no reports on this aspect.