Epilepsy, the term used to describe the repeated occurrence of the various forms of convulsive seizures, is one of the oldest afflictions known to man. It has been a subject of discussion in medical and lay literature since long.

During the period of Greek enlightenment, Hippocrates (1849) suggested that the etiology of epilepsy did not lie in the realm of the supernatural, but could be attributed to the natural biological causes, primarily heredity. Many studies have been conducted over the years in an attempt to assess the role of genetic factors in epilepsy. Lennox (1951), in a study of 20,000 relatives of 4,231 epileptic patients found that both in the essential (hereditary) and symptomatic type of epilepsy there was evidence of increased familial predisposition, i.e., the prevalence of epilepsy in the near relatives of both groups of patients was significantly increased as compared with the general population. Furthermore, the prevalence of epilepsy in the near relatives of the essential group was higher than that in the near relatives of the symptomatic group. These studies
have been subsequently confirmed by Lennox and Jolly (1954), Lennox (1960), Harvald, (1954) and Metrakos (1960). Based on the family studies, Lennox (1960) concluded that the division between idiopathic and symptomatic epilepsy is not clear cut, and that both genetic and environmental factors are operative in varying degrees in every epileptic patient.

Alstrom (1950) in a study of 897 epileptic patients showed that the prevalence of seizure in first-degree relatives of epileptics was not significantly higher than that in general population. Penfield and Paine (1955) in a study of 224 patients with temporal lobe epilepsy, concluded that hereditary tendency could be ruled out as a factor in the development of focal cortical seizures. Eisner et al. (1959; 1960), in a study of 669 epileptics and 470 control families, surmised: "hereditary transmission of epilepsy could not be demonstrated, but could also not be ruled out". However, it was only after EEG came into general use, as a tool in these studies, that more precise conclusions could be drawn.
Classification of Seizures:

The clinical manifestations of seizure include a bewildering array of sensory, motor and autonomic phenomena. The observable presentation of these disturbances in the functioning of central nervous system is, at present, the only basis on which a working classification of seizures can be constructed (Gastaut, 1970). This, in fact, is not a classification of epilepsies. A patient can have epilepsy, which may manifest itself in several patterns of seizures. The international classification attempts to describe such seizures in relation to six aspects: (1) the clinical seizure type; (2) electroencephalographic seizure type (EEG pattern during a seizure); (3) electroencephalographic interictal expression (EEG pattern between clinical seizures); (4) anatomical substrate; (5) etiology, and (6) age.

Four major categories of seizures are recognized:

I. Partial Seizures: In which the clinical manifestations initially indicate local activation of a functional and/or anatomical group of neurons. These are further subdivided as partial seizures
with elementary symptoms, partial seizures with complex symptoms, and partial seizures secondarily generalized.

II. Generalized Seizures: Seizures in which the clinical features do not include any sign of symptom referable to an anatomical and/or functional system localized in one hemisphere, and usually consist of initial impairment of consciousness, motor changes which are generalized or at least bilateral and more or less symmetrical and may be accompanied by an "en masse" autonomic discharge; in which the electroencephalographic patterns from the start are bilateral, grossly synchronous and symmetrical over the two hemispheres; and in which the responsible neuronal discharge takes place, if not throughout the entire grey matter, at least in the greater part of it, and simultaneously on both sides (Masland, 1975). Eight categories are recognized: (1) absence (petit mal); (2) bilateral massive epileptic myoclonus; (3) infantile spasms; (4) clonic seizures; (5) tonic seizures; (6) tonic-clonic seizures
(grand mal); (7) atonic seizures; and (8) akinetic seizures.

III. Unilateral or predominantly unilateral Seizures:
Unilateral seizures are tonic-clonic or clonic which may or may not be associated with loss of consciousness and which principally are restricted to one side of the body with paroxysmal electroencephalographic activity in the contralateral hemisphere.

IV. Unclassified Seizures: These are seizures in which the relevant information is insufficient to allow classification into the other categories.

Mode of Inheritance

There are specific modes of inheritance into which the various forms of epilepsy can be classified. The main types are: single gene and polygenic. There are more than 100 single-gene disorders in the McKusiek (1975) classification of genetic diseases that may be associated with seizures (Anderson, 1978; and Metrakos, 1978). Examples include autosomal dominant disease, such as, tuberous sclerosis and neurofibromatosis;
various degenerative diseases of the CNS such as Tay-Sachs disease and cerebromacular degeneration, as well as, a number of amino acid pathies, all of which are inherited as autosomal recessive traits; and several x-linked conditions, such as Menkes Syndrome. Chromosomal anomalies in which cerebral seizures may constitute a part of the clinical syndrome include trisomies 13 and 18, and deletion of the long arm of chromosome 21 (Metrakos, 1978).

Based on the findings in families of patients with focal epilepsy, 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. Thus, one or more major genes or polygenes interact with maturational and endocrine factors, resulting in age and sex differences, as well as, with various exogenous environmental factors, to produce a variety of clinical and EEG findings.

**Neurochemistry**

The earliest studies focussed principally on energy metabolism in relation to oxygen supply, glucose
metabolism and oxidative phosphorylation. The relationship of available energy supply to the maintenance of ionic gradients across neuronal membranes developed from this, and more recently the role of glial cells in the maintenance of ionic homeostasis has been emphasized. The role of possible neurochemical transmitter substances has received more attention.

A. **Energy metabolism**

The principal substrate for energy metabolism in the brain is glucose. In order to meet this demand the brain receives about 20% of the total cardiac output and utilizes 20% of the total body oxygen consumption along with more than 50% of the total body glucose consumption. Energy derived from the oxidation of glucose is stored as phosphocreatine and utilized as adenosine triphosphate (ATP). As much as 50% of the available energy supply may be used for the maintenance of intracellular-extracellular cation gradients. The oxidation of two carbon fragments in CNS is mediated by citric acid cycle. However, a unique metabolic pathway, the γ-aminobutyric acid (GABA) shunt also exists. Thus, in addition to the usual oxidative pathway from
\(\alpha\)-ketoglutarate to succinate, an alternate pathway consists of transamination of \(\alpha\)-ketoglutarate to glutamate, decarboxylation of glutamate to GABA, transamination of GABA to succinic semialdehyde followed by dehydrogenation to succinate. Glutamic acid occupies a key position in the metabolism of CNS. Transaminations with pyruvate or oxaloacetate provide access to citric acid cycle via \(\alpha\)-ketoglutarate. Decarboxylation by glutamic acid decarboxylase, a vitamin B\(_6\)-dependent apoenzyme, produces GABA, which appears to be an important inhibitory modulator or transmitter substance. As the substrate for the reversible formation of glutamine, glutamate is also important for ammonia metabolism, a variety of manipulations of glutamic acid metabolic pathway produce increased or decreased seizure susceptibility. For example, depletion of the B\(_6\) vitamin (pyridoxal 5-phosphate) by a number of methods (dietary depletion, inactivation, competitive antagonism) has been shown to produce convulsions in animals and man. In this situation depletion of GABA occurs primarily because the affinity of glutamic acid decarboxylase for the B\(_6\) vitamin is considerably less than that of
the transaminases. Hypoglycemia is a well established cause of seizures, and the potential role of glutamic acid in cerebral energy metabolism is emphasized by the fact that only glutamic acid can replace glucose in the maintenance of energy metabolism.

B. **Electrolytes**

The normal neuronal resting membrane potential results from the maintenance of an intracellular electrolyte concentration that is high in $K^+$ and low in $Na^+$ relative to the extracellular fluid concentration. Energy is utilized by an electrolyte transport system in the neuronal membrane, $Na-K$, $Mg, ATPase$, to maintain these gradients. With excitatory-postsynaptic depolarization sufficient to produce an action potential, $Na^+$ moves intracellularly and $K^+$ flows out. During repolarization, $Na^+$ extrusion is coupled with $K^+$ uptake and the utilization of ATP to reestablish the membrane potential. Inhibitory postsynaptic potentials hyperpolarize the neurone and an action potential is not generated. Deficiencies in the supply of the available ATP or functioning of the $Na-K$, $Mg-ATPase$ system would lead to intracellular accumulation of $Na^+$, lowering of
membrane potential, and enhanced excitability. This has been shown experimentally, with ouabain, adrenalectomy, hypoglycemia, extracellular K⁺ perfusion, and a variety of other procedures.

Depolarization of the presynaptic ending results in the release of a chemical transmitter substance which then influences the post-synaptic membrane to produce a localized change in membrane potential. Any event that alters the synthesis, release, sensitivity, or inactivation of neurotransmitter, affects the excitation or inhibition mediated by the compound.

Keeping in view all these facts, it can be appreciated 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, an effective anticonvulsant drug should stabilize neuronal membranes, augment inhibitory processes, or suppress excitation.

The effect of anticonvulsant drugs on conduction and synaptic transmission in peripheral nerves reflects
some of the properties of these drugs observed in the CNS. Normal conduction in a peripheral nerve is unaffected by either phenobarbital or phenytoin, except at very high concentrations. However, hyperexcitability induced in peripheral nerve by either chemical or electrical stimulation is suppressed by phenobarbital and phenytoin, in contrast to trimethadione, which does not exhibit such an effect. Phenobarbital and phenytoin differ in their action on synaptic transmission in peripheral nerve and in the central nervous system (Esplin, 1972). Barbiturates decrease excitatory postsynaptic potentials without altering the resting membrane potential. Barbiturates also prolong synaptic recovery time. Hydantoins have no influence on monosynaptic transmission. Trimethadione and carbamazepine do not affect monosynaptic transmission, while acetazolamide does cause suppression. In contrast to its effect on monosynaptic pathways, acetazolamide has no effect on polysynaptic pathways and, in the same manner, carbamazepine which does not influence monosynaptic transmission, does increase the latency and reduce the response in polysynaptic pathways. The benzodiazepines suppress both types of transmission.
Role of Cyclic Nucleotides

There is ample evidence that cyclic adenosine 3',5'-monophosphate (cAMP) and cyclic guanosine 3',5'-monophosphate (cGMP) are biologically significant compounds in the central nervous system (CNS) (Bloom, 1975; Daly, 1977; and Phillis, 1970). Of particular relevance to the present subject are the observations that neuronal activity markedly influences cyclic nucleotide regulation in brain (Daly, 1977; and Ferrendelli, 1976). It is now well documented that agents that cause cellular depolarization, e.g., ouabain, veratridine, glutamate, or high levels of extracellular K+, cause marked elevations of cAMP and cGMP levels in incubated brain slices from all animal species studied, including man. In addition, experimental seizures produced by many convulsant drugs or other seizure-inducing procedures elevate the levels of both cyclic nucleotides in brain, in vivo (Ferrendelli and Kinscherf, 1977; Lust et al., 1976; and Stattin, 1971). Although, the mechanism responsible for the elevation of cyclic nucleotides in epileptic brain is not clear, the following explanation has been put forward.
During cellular depolarization, there is an augmented influx of calcium into intracellular spaces. It is believed that the increased free intracellular calcium leads to elevated cAMP levels. Cellular depolarization also results in augmented release of neurotransmitters or neuromodulators from intracellular stores, and the subsequent action of these elevated cAMP levels by activating specific membrane bound adenylate cyclases. Elevated cGMP levels may have some role in sustaining seizure discharge since recent observations have demonstrated that this nucleotide can cause cellular depolarization (Stone et al., 1975) and seizure discharge (Hoffer et al., 1977). At present, the significance of elevated cAMP levels in the brain of epileptics is not clear.

The observation that seizures are associated with altered cyclic nucleotide levels in brain suggests the possibility that these compounds may be involved in the mechanism of action of antiepileptic drugs.
Effect of antiepileptic drugs on cyclic nucleotide elevations produced by seizures or cellular depolarization

Phenytoin, carbamazepine, and several other antiepileptic drugs have selective activity against maximal electroshock seizures (MES) and are particularly effective for the treatment of generalized tonic-clonic convulsions. In contrast, ethosuximide, trimethadione and valproic acid, drugs of choice for treatment of 'absence seizures' have preferential activity against pentylenetetrazol (metrazol) seizures but have less or no anti-MES activity. Some drugs especially barbiturates, possess both anti-MES and anti-metrazol activity and may be used to treat several types of clinical seizures. It has been found that phenytoin and phenobarbital, two drugs with similar potent anti-MES activity, inhibited accumulation of calcium by isolated nerve terminals (synaptosomes), but ethosuximide, which is devoid of anti-MES activity, had no effect (Sohn and Ferrendelli, 1976).

It has also been observed that drugs with anti-MES activity inhibited depolarization induced accumulation
of both cAMP and cGMP in incubated slices of mouse cerebral cortex (Ferrendelli and Kinscherf, 1979). In contrast, e-thosuximide, trimethadione, valproic acid, low concentration of clonazepam and drugs with predominant anti-metrazol activity, were ineffective in this system or inhibited accumulation of only cGMP.

**Physiological Disposition of Anticonvulsants**

The physiological disposition of a drug, i.e., how a drug is handled by the body, how it is absorbed into the blood stream, how it disperses in body tissues, how it is metabolized and excreted, is one of the principal determinants of the intensity and duration of action.

Of the A D B E (absorption, distribution, bio-transformation and excretion) factors, the completeness of absorption is one of the most important factors in determining the plasma level. Absorption depends on a host of physical and chemical factors such as solubility, disintegration and dissolution rates of solid drugs, particle size, pH of gastrointestinal fluids, pKa of the drug, Ca/PO₄ ratio,
bile salt concentration, amount of food present, etc. Another important factor is the apparent volume of distribution of drugs which depends on various factors, e.g., the size and extent of penetration by the drug of the extracellular and intracellular compartments, involvement of active transport, and possible binding to inactive sites. The rate of elimination of anti-convulsant drugs is probably the most important factor in regulating the plasma level. Elimination occurs either, by biotransformation of drugs from the active to the inactive form or by excretion in the urine or faeces, or by both the processes. The intensity of the effect of the drug on the receptor is altered by such factors as the functional state of the body, pathological disturbances, development of tolerance, and the presence of other drugs. It is apparent, therefore, that the enormous individual differences in the relation between the dosage of a drug and the intensity of its pharmacological action are a result of many factors which influence the steps between dosage and action. The half life refers to the rate at which the drug is removed from the serum compartment and actually represents a combination of the speed of
metabolism of that drug by the liver and the rate of excretion of the unchanged drug directly by the kidneys. Pharmacokinetic principles are useful only in so far as the data used to formulate the dosage schedules are reliable. The most critical need concerns accurate biological half-life data for drugs and their metabolites.

**Drug interaction**

The administration of other drugs simultaneously with antiepileptic drugs may alter the clinical response to the usual therapeutic doses in many ways. They may increase the biotransformation of the drug by inducing the enzyme-system in the endoplasmic reticulum of the liver concerned with metabolism of drugs (Mannering, 1971). This would reduce the plasma level of the drug and decrease its half-life. Usual doses would not, therefore, give the same response. Many drugs can induce this system, and lower antiepileptic drug levels. Among these are the barbiturates, particularly phenobarbital, ethanol, DPH, DDT and griseofulvin. Induction of liver drug metabolizing enzymes does not always decrease the therapeutic response since many antiepileptic drugs are biotransformed.
into products that are also active antiepileptics. For example, TMO is converted by the liver into its N-dimethylated derivative, dimethadione (DMO), which has anticonvulsant activity slightly higher than that of TMO. Enzyme induction by another drug might actually enhance the effect of TMO by increasing the amount of DMO, although the plasma level of TMO would be decreased. Other examples are primidone, which is converted by the liver to phenobarbital and phenylethylmalonamide (PEMA), both of which are active anticonvulsants (Gallagher and Baumel, 1972), and diazepam which is biotransformed to oxazepam and other metabolites which possess anticonvulsant activity.

Other drugs may cause inhibition of the drug metabolizing system in the liver. In this case, the plasma levels and half-lives increase and toxicity often occurs. Examples of this are the effect of sulthiame, disulfiram, phenyramidol and isoniazide to inhibit the biotransformation of DPH.

Alteration of the therapeutic response to an antiepileptic agent in conjunction with other drugs can also result from a competition for plasma binding
sites. Only 10% of the DPH administered is available in the free form since about 90% binds to plasma proteins. The free level of DPH in plasma can be increased by administration of salicylates, thyroxine, phenylbutazone and others that compete for the binding site of the protein. Interactions of the drugs may also occur at the receptor level, altering the therapeutic response (Woodbury, 1969).

Sister Chromatid Exchange

Sister Chromatid Exchanges (SCEs) represent an interchange of DNA between replication products at apparently homologus loci. Such exchanges which are generally detected in cytological preparations of metaphase chromosomes, presumably involve breakage and reunion, although the molecular basis of SCE remains obscure. It has been used to detect the effect of various chemical and physical agents on chromosomes and to differentiate between different chromosome fragility diseases.

SCEs were first described by Taylor et al. (1957) using autoradiography to detect differentially labelled sister chromatids in cells that had undergone
one cycle of tritium labelled thymidine (3HdT) incorporation followed by a replication cycle in nonradioactive medium. In extensive studies on SCE phenomenon Taylor (1958, 1959) arrived at some important conclusions: (1) SCEs can occur spontaneously; (2) each chromatid is composed of one DNA duplex; (3) the rejoining of subunits of a chromatid is not random, but strictly restricted to those having same polarity, and (4) SCEs involve a double strand exchange.

The recent development of techniques for demarcating sister chromatids without using 3H-thymidine is due greatly to the pioneering work of Zakharov and Egorina (1972). They showed that when cells were grown in the presence of 5-bromo-deoxyuridine (BUdR) for two cell cycle rounds, two chromatids could be distinguished from each other by their unequal spiralization patterns. They also found that one of the chromatids occasionally appeared as a weakly stained thread by Giemsa. These results were confirmed by Ikushima and Wolff (1974), who showed that when chromosomes had
incorporated BUdR or 5-Iododeoxyuridine (I UdR) into their DNA during two replication cycles, the chromatids that contained BUdR (or IUdR) in both DNA strands stained lighter than their sister chromatids in which only one of the strands had been replaced with halo-
genated analog. In 1973, Latt reported a new method which consisted of staining BUdR substituted chromosomes with the fluorochrome Hoechst 33258 and studied under fluorescence microscope. As the substitution of thymidine with bromouracil in chromosomal DNA causes a reduction in the fluorescence of this dye, a bifilarly substituted (BFS) chromatid fluoresces lighter than a unifilarly substituted (UFS) chromatid. The disadvantage of this method, however, is that the image of differentially fluorescing chromatids fades very rapidly. The use of another fluorescent dye, acridine orange, appears to eliminate this problem to a certain degree (Dutrillaux et al., 1974; Franceschini, 1974; Kato, 1974d; and Perry and Wolff, 1974). To overcome these disadvantages, Perry and Wolff (1974) developed a modified method which they called the fluorescence plus Giemsa (FPG) technique. It consists of staining chromosomes with Hoechst 33258,
exposing them to daylight for 24 hours, followed by incubation in distilled water or in a salt solution for two hours at 60°C prior to the permanent staining with Giemsa. Many modifications of this technique are now available. Kim (1974) reported a method in which the incubation step used in the FPG technique was omitted. Without prestaining with Hoechst 33258, Giemsa staining alone was found to result in the appearance of clearly differentiated sister chromatids when slides were preheated for 10 minutes at 67°C in 1 M Na₂HPO₄ (Korenberg and Freedlander, 1974).

Hoechst 33258 can be replaced by various metachromatic dyes such as thionine and toluidine blue (Goto et al., 1975). Furthermore, it has been shown that techniques for revealing chromosomal bands, such as trypsin and urea treatment, are equally effective in differential Giemsa staining of Sister Chromatids (Pathak et al., 1975). The staining methods thus vary greatly in the different techniques described above. Nevertheless, they are effective only when applied to BUdR- (or IUdR)-substituted chromosomes. For this reason, all these techniques are referred to as BUdR-labelling methods.
However, demarcation is also possible between unsubstituted and UFS chromatids in cells grown for one round of replication in the presence of, and another round in the absence of BUdR in the culture medium (Kato, 1974d,f; and Kihlman and Kronborg, 1975). To promote the uptake of BUdR by cells, the labelling of chromosomes is often carried out in the presence of fluorodeoxyuridine (FUdR) and uridine (Chaganti et al., 1974; Latt, 1974a,b; and Kihlman and Kronborg, 1975).

Reasons for Differential Staining:

Zakharov and Egolina (1972) noted that after Giemsa staining the pale chromatid was usually longer than its sister counterpart. They postulated that protein synthesis which affects chromosome condensation and spiralization was delayed due to the substitution of thymidine by BUdR. Since, proteins are more lightly bound to DNA containing BUdR than to unsubstituted DNA (David et al., 1974), Ikushima and Wolff (1974) attributed the differential staining
to a differential binding of protein to the DNA of chromatin. Experiments have been carried out by Wolff et al. (1977) in which slides were exposed to very intense light from a high-pressure mercury burner followed by staining in Giemsa. This resulted in dramatic harliquinization. Light can break disulfide bonds in protein (Mousseron-Canat et al., 1972). Further, experiments with chemical agents that can break disulfide bonds, e.g., dithiothreitol or β-mercaptoethanol when incubated with cells in dark prior to staining with Giemsa also led to differential staining of the sister chromatids (Wolff et al., 1977). These studies also implicate differential compaction of the chromosome influenced by the binding of nonhistone proteins in the differential staining. Latt (1973) showed that the fluorescence of Hoechst 33258 is much less efficient when the dye is bound to poly (dA-BUdR), as compared with poly (dA-dT), and has suggested that the difference observed between the
two sister chromatids is due to a differential quenching of fluorescence by BUDR. However, the fact that Giemsa stainability is also different in these chromatids (Zakharov and Egolnia, 1972; and Ikushima and Wolff, 1974), implies that the mechanism is somewhat more complicated. Various G-banding procedures, such as, the treatment with salt solution (Korenberg and Freedlander, 1974), and with trypsin (Pathak et al., 1975) facilitate the differential staining of sister chromatids with Giemsa. This suggests an interaction between the dye and the molecular architecture of BUDR substituted chromosomes.

A number of investigators have attempted to localize SCEs in chromosome banding patterns. For example, in human chromosomes, SCEs appear to occur preferentially either, in between quinacrine (Q)-positive bands or, at the junction of Q-positive and Q-negative regions (Latt, 1974a). Subsequent studies detected a clustering of SCEs at the junctions between heterochromatic and euchromatic regions in chromosomes, e.g., in muntjac (Carrano and Wolff, 1975) and Kangaroo rat (Bostock and Christie, 1976). The
significance of these "junctional" regions is not yet clear. It has also been reported that SCEs occur preferentially with heterochromatic arms of Microtus chromosomes (Natrajan and Klasterska, 1975) and human chromosomes (Schned et al., 1976). Dubos (1978) used three staining techniques (G, Q and R banding), consecutively to localize the breakage points in chromosomes of human lymphocytes. It was found that about 85% of the breaks occurred at the interbands between R- and Q-bands. The reason for the occurrence of these breaks in the interband regions is not yet clear.

**Sister Chromatid Exchanges as Indicator of Mutagenicity**

A mutagen is an agent that induces mutation and mutation is a transmissible alteration of the genetic information. The determination of the mutagenicity of a given agent reveals only a mutagenic potential, which is expressed in a biological system. This potential can be masked by efficient detoxication. Many genetic effects are not the direct result of the interaction of a mutagen with the genetic material but rather the end-product of complex metabolic
The frequency of SCEs has proved to be a very sensitive indicator of the effect of chemical mutagens and carcinogens on eucaryotic chromosomes. The first study was carried out by Latt on human lymphocyte chromosomes treated with mitomycin C that cross links DNA (Latt, 1974). Large number of SCEs were observed at chemical concentrations too low to induce chromosomal aberrations, and it was suggested that the sensitivity of the system was such that it would have great utility as a test system for the effect of mutagens on mammalian chromosomes. Of particular interest is the extensive study carried out by Perry and Evans (1975). They tested Chinese hamster ovary cells with 14 known or suspected mutagens/carcinogens and found that all the direct-acting mutagens showed an enhanced frequency of SCEs. With the exception of Adriamycin and bleomycin which are chemotherapeutic agents, no induction of chromosome aberrations was found at low concentrations that could increase the incidence of SCEs by a factor of 10. The only chemicals that did
not increase the SCEs in this system in vitro were maleic hydrazide (which is not mutagenic in mammalian cells) and the chemotherapeutic agent cyclophosphamide (which requires metabolic activation to be effective).

**Sister Chromatid Exchange and Human Genetic Diseases**

Three human genetic diseases, Fanconi's anemia, Bloom's syndrome and ataxia telangiectasia, are characterized by a high incidence of chromosome aberrations and a concomitant increased susceptibility to cancer. In cells from patients with Fanconi's anemia (Latt et al., 1975; Chaganti et al., 1974; Sperling et al., 1975; and Kato and Stich, 1976). and ataxia telangiectasia (Galloway and Evans, 1975; and Chaganti et al., 1974), the frequency of SCEs is normal. But in cells from patients with Bloom's syndrome SCEs are ten to thirteen times more than the normal population. Normal number of SCEs also occur in cells from patients with DNA-repair-deficient human disease, xeroderma pigmentosum (Wolff et al., 1975) and Warner's syndrome (Bartram et al., 1976). The xeroderma pigmentosum cells seem to be sensitive to induction of SCEs by
chemical agents, without any concomitant increase in chromosomal aberrations. On the other hand, cells from patients suffering from Fanconi's disease show equal incidence of both SCEs and chromosomal aberrations when treated with mitomycin C (Latt et al., 1975). Based on the differential response of these diseases in terms of SCEs and chromosomal aberrations Latt et al. (1981) suggested that two different mechanisms might be responsible for their induction.

**Mutagenic and Teratogenic Effect of Anticonvulsant Drugs**

There seems to exist no antiepileptic drug of which the intake during pregnancy has not been followed by the birth of a child with congenital abnormalities (German et al., 1970a,b; Speidal and Meadow, 1972; and Meyer, 1973). This is true not only for barbiturates and hydantoins but also for oxalozidines (German et al., 1970a,b; and Speidal and Meadow, 1972), succinimides (Lowe, 1973; Starreveld-Zimmerman et al., 1973; and Meyer, 1973), benzodiazepines (Speidal and Meadow, 1972), acetyl urea (Speidal and Meadow, 1972) and carbamazepine
(Meyer, 1973). Since in most cases a combination of drugs has been prescribed, a casual relationship to a particular drug becomes difficult to establish.

Treatment of epilepsy with antiepileptic drugs is usually for a long duration. Anticonvulsants such as primidone, diphenylhydantoin, and carbamazepine are suspected to be mutagenic and teratogenic (Ayraud et al., 1968; Neuhauser et al., 1970; Grosse et al., 1972; Annegers et al., 1974; Hanson and Smith, 1975; Janz, 1975; Herha and Obe, 1976). DPH which is also an anticonvulsant drug, has been reported to be teratogenic in mice (Massay, 1966; Gibson et al., 1968; and Harvison et al., 1969). Some reports suggest that it may have some similar action in man as well (Speidal et al., 1972; and Monson et al., 1973). Most studies are in agreement that epileptic mothers receiving anticonvulsants are two to three times more likely to have malformed infants than normal mothers (Meyer, 1972; Annegers et al., 1974; Janz, 1975; and Shapiro et al., 1976). There are also reports showing a greater number of anomalies in treated epileptics than in untreated patients (South,
1972; Lowe, 1973; and Monson et al., 1973). Several short communications suggesting teratogenicity of anticonvulsants acknowledge the inadequacy of data in this regard (Speidal et al., 1972; Monson et al., 1973; Fedrick, 1973; and Hill, 1976). Thus, there is no statistical proof of a casual relationship so far reported between anticonvulsants and malformations.

Some of the serious types of malformations commonly observed are cleft lip, cleft palate, congenital heart disease, mental deficiency and microencephaly in the offsprings of epileptics (Hill et al., 1974; and Janz, 1975). These have been attributed to the use of anticonvulsants. However, the results of two studies, one in Finland and another in USA raise the possibility that fetal damage may be due to epilepsy itself (Shapiro et al., 1976). In USA, drug exposure information was collected before delivery in a cohort of 50232 mother/child pairs. The total malformation rate in 305 children born to epileptic mothers was 10.5% as against 6.4% in the remainder. When the fathers had epilepsy, the malformation rates in their children are found to be
intermediate. There is a greater prevalence of anomalies in relatives of epileptics (Starreveld-Zimmerman et al., 1975; and Waziri et al., 1976). Conversely there is also a high rate of epilepsy in families with cleft lip and palate (Dronamraju, 1970). The increased incidence of anomalies in offspring of epileptic fathers (Meyer, 1973; Shapiro et al., 1976) may be an evidence of dysmorphic tendencies in these families. This may be a genetic tendency or it may represent a mutagenic effect of drugs before pregnancy.

Since teratogenicity has been related to chromosomal breakage, studies have been performed to find out whether anticonvulsants have any similar cytogenetic effects on human lymphocytes.

Reports on the effect of anticonvulsant drugs on human chromosomes have been quite contradictory. Muniz et al. (1969) and Brøgger (1970) found no significant chromosomal breaks in vitro in the therapeutic range of DPH (Muniz et al., 1969) and ethotoxin (Brøgger, 1970). In the toxic range (50 to 100 μg/ml), however, significantly frequent chromosomal breaks
occurred (Muniz et al., 1969). So far as in vivo studies are concerned, no structural anomalies were reported in the chromosomes of lymphocytes from seven epileptics on dilantin at a therapeutic level (1-20 μg/ml). Brogger (1970), however, reported that one boy being treated with ethosuximide showed numerous chromosomal aberrations, chromatid breaks and gaps at toxic level of the drug. Ayraud et al. (1968) showed chromosomal breaks in a girl and her mother who was treated with antiepileptic drugs during pregnancy. Other studies (Caratazali and Roman, 1969, 1971) showed an inhibiting effect of DPN and barbiturates on mitosis in vitro. Roman and Caratazali (1971) reported chromosomal abnormalities in mice treated with phenytoin and primidone. It was considered that the chromosomal abnormalities induced by anticonvulsant drugs are caused either by the inhibition of folic acid synthesis (which is one of the precursor of inosine synthesis playing a fundamental role in purine synthesis), or by the inhibition of the synthesis of protein constituents of the chromosomal matrix, thus interfering with the normal development of mitosis (Roman and Caratazali, 1971). Marquez-
Monter et al. (1970) studied peripheral blood lymphocytes from 20 epileptic patients on sodium hydantoinate (200-400 mg/d) treatment and noted an increase in the frequency of tetraploid and hypotetraploid cells (2-18%; average 5.4%). But no correlation between the alteration in chromosomal number and duration of the treatment has been observed. Neuhauser et al. (1970) have described an increased number of metaphases with structural aberrations in five female epileptic patients treated with various anticonvulsant drugs, including DPH and in their children exposed to these drugs during pregnancy. The most comprehensive study was done by Grosse et al. (1972). Their results showed that the rate of structural chromosomal abnormalities of 32 epileptic mothers and their children with an age up to three years, who were exposed to antiepileptic drugs in utero, was significantly higher than in the untreated healthy controls. There was a significant correlation between the aberration-values of the mothers and their children. A higher frequency of chromosomal aberrations in children born to mothers on therapy with various anticonvulsants reported may be considered a dose dependent effect,
since the average daily dose of drugs taken by the mothers is approximately twenty times higher, per kg body weight, for the fetus as compared with the mother (Neuhauser et al., 1970; and Grosse et al., 1972).

Stenchever and Allen (1973) studied the in vitro effect of three anticonvulsant drugs, phenytoxin, primidone and mephenytoin on the chromosomes of human (one female and one male) leukocytes at 100, 10, 1.0 and 0.1 μg/ml concentration. No significant increase in chromosomal breaks and gaps could be observed for any of the drugs studied, compared with the controls. Bishun (1975) investigated the effect of various anticonvulsants (phenytoin, mepatol and zarontin) on the chromosomes in human lymphocytes. He observed no apparent chromosomal abnormalities (breaks, rearrangements etc.) produced by these drugs at the concentration of 10, 20, 40, 50 and 70 μg/ml. But, any increase in the concentration beyond 70 μg/ml inhibited mitosis. Further, Bartsch (1975) found no elevation of chromosomal aberrations in lymphocytes from children on monotherapy with phenytoin and primidone. On the other hand, Herha and Obe (1976, 1977)
reported that anticonvulsant drugs induced an elevation of chromosomal damage. However, since the patients received a combination of different anticonvulsant drugs it was not possible to ascertain any difference in the clastogenic effects of the various anticonvulsants.

Recent studies by Alving et al. (1976, 1977), Knuutila (1977), Kotlarek and Faust (1978) and Esser et al. (1981) are in agreement, that at therapeutic levels, anticonvulsant drugs do not produce chromosomal abnormalities.

In 1976, Alving et al. repeated the work of Muniz et al. (1969) but were unable to confirm their results in in vitro experiments, nor could they find any evidence of chromosomal damage in bone marrow cells from rats treated with large doses (50 mg/kg body weight once a day for three days) of DPH. Further, Alving et al. (1977) studied chromosomes both in bone marrow cells and peripheral blood leukocytes from epileptic patients (4 male + 6 female, age range 19-49 years, mean 33 years) on DPH treatment (4-20 years, mean 11 years) alone. No significant increase
either in metaphases with structural abnormalities or in hyperdiploid metaphases in treated patients compared with the controls could be shown. Knuutila et al. (1977) studied 22 epileptic patients (age ranging from 4-47 years with a mean of 21), all of whom were severely retarded both physically as well as mentally. All the patients had been treated with only phenytoin for at least 6 months. During this time the dose of phenytoin was at a level where convulsions ceased to occur. The effective doses of serum phenytoin concentration varied between 4 and 113 μ mol/l. At therapeutic level of the drug no significant abnormalities could be noticed in the bone marrow cells. In 1978, Kotlarek and Faust noted in ten patients (age 4-13 years) with pyknolepsy on dipropylacetate monotherapy (duration 6-44 months, dose 25-40 mg/kg body weight), that no increase in chromosomal aberrations as compared with the controls could be produced by anticonvulsant monotherapy.

Most recently Esser et al. (1981) performed studies on 20 epileptic patients (age range 3-15 years), ten on phenytoin (duration 8-28 months,
dose 4.8 - 26.4 µg/ml) and remaining 10 on primidone (duration 17-26 months, dose 1.9 - 13.5 µg/ml) but did not observe any significant increase in chromosomal aberrations in groups of patients on therapy with either primidone or phenytoin compared with the controls. It was proposed that absence of a significant increase in chromosomal aberrations in this study could be due to a better DNA-repair capacity in children, which is in accordance with the findings of Niedermuller (1978) who described a higher DNA-repair capacity in younger rats.