



Adverse effect is 'any undesirable or unintended consequence of drug administration'. It is a broad term, includes all kinds of noxious effect—trivial, serious or even fatal.

For the purposes of detecting and quantifying only those adverse effects of a drug which are of some import and occur in ordinary therapeutic setting, the term *adverse drug reaction* (ADR) has been defined as 'any noxious change which is suspected to be due to a drug, occurs at doses normally used in man, requires treatment or decrease in dose or indicates caution in the future use of the same drug'. This definition excludes trivial or expected side effects and poisonings or overdose.

Another term '*adverse drug event*' (ADE) has been used to mean 'any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with the treatment'. The idea is to record all adverse events first, and look for causality only while analyzing pooled data.

All drugs are capable of producing adverse effects and whenever a drug is given a risk is taken. The magnitude of risk has to be considered along with the magnitude of expected therapeutic benefit in deciding whether to use or not to use a particular drug in a given patient, e.g. even risk of bone marrow depression may be justified in treating cancer while mild drowsiness caused by

an antihistaminic in treating common cold may be unacceptable.

Adverse effects may develop promptly or only after prolonged medication or even after stoppage of the drug. Adverse effects are not rare; an incidence of 10–25% has been documented in different clinical settings. They are more common with multiple drug therapy and in the elderly. Adverse effects have been classified in many ways. One may divide them into:

Predictable (Type A or Augmented) reactions (mechanism based adverse reactions) These are based on the pharmacological properties of the drug, which means that they are augmented, but qualitatively normal response to the drug; include side effects, toxic effects and consequences of drug withdrawal. They are more common, dose related and mostly preventable and reversible.

Unpredictable (Type B or Bizarre) reactions These are based on peculiarities of the patient and not on drug's known actions; include allergy and idiosyncrasy. They are less common, often non-dose related, generally more serious and require withdrawal of the drug. Some of these reactions can be predicted and prevented if their genetic basis is known and suitable test to characterize the individual's phenotype is performed.

Severity of adverse drug reactions has been graded as:

Minor: No therapy, antidote or prolongation of hospitalization is required.

Moderate: Requires change in drug therapy, specific treatment or prolongs hospital stay by at least one day.

Severe: Potentially life-threatening, causes permanent damage or requires intensive medical treatment.

Lethal: Directly or indirectly contributes to death of the patient.

Pharmacovigilance

Pharmacovigilance has been defined by the WHO as the 'science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.' The information generated by pharmacovigilance is useful in educating doctors about ADRs and in the official regulation of drug use. It has an important role in rational use of medicines, as it provides the basis for assessing safety of medicines.

The activities involved in pharmacovigilance are:

- a. Postmarketing surveillance and other methods of ADR monitoring such as voluntary reporting by doctors (e.g. yellow card system of UK), prescription event monitoring, computerized medical record linkage and other cohort/case control studies as well as anecdotal case reports by doctors.

Voluntary reporting depends on the initiative and willingness of the health professionals. It is minimal in India, while even in the developed countries only ~10% ADRs are reported voluntarily. Generally, immediately occurring reactions and those that are dramatic are reported. Though even rare reactions can be detected by this method, it does not provide incidence of the reaction.
- b. Dissemination of ADR data through 'drug alerts', 'medical letters,' advisories sent to doctors by pharmaceuticals and regulatory agencies (such as FDA in USA, committee on safety of medicines in UK).
- c. Changes in the labelling of medicines indicating restrictions in use or statutory warnings, precautions, or even withdrawal of the drug.

Pharmacovigilance centres have been set up in most countries. The Uppsala Monitoring Centre (Sweden) is the international collaborating centre. In India, the national coordinating centre is located in the All India Institute of Medical Sciences. Regional centres are expected to collect, communicate and disseminate ADR data by linking with medical institutions and practitioners. The pharmacovigilance centres are also expected to provide expertise for assessing causality and severity of ADRs by using standard algorithms and rating scales.

Prevention of adverse effects to drugs Adverse drug effects can be minimized but not altogether eliminated by observing the following practices:

1. Avoid all inappropriate use of drugs in the context of patient's clinical condition.
2. Use appropriate dose, route and frequency of drug administration based on patient's specific variables.
3. Elicit and take into consideration previous history of drug reactions.
4. Elicit history of allergic diseases and exercise caution (drug allergy is more common in patients with allergic diseases).
5. Rule out possibility of drug interactions when more than one drug is prescribed.
6. Adopt correct drug administration technique (e.g. intravenous injection of vancomycin must be slow).
7. Carry out appropriate laboratory monitoring (e.g. prothrombin time with warfarin, serum drug levels with lithium).

Adverse drug effects may be categorized into:

1. Side effects

These are unwanted but often unavoidable pharmacodynamic effects that occur at therapeutic doses. They can be predicted from the pharmacological profile of a drug and are known to occur in a given percentage of drug recipients. Reduction in dose generally ameliorates the symptoms.

A side effect may be based on the same action as the therapeutic effect, e.g. atropine is used in preanaesthetic medication for its antisecretory action. The same action produces dryness of mouth as a side effect. Acetazolamide acts as a diuretic by promoting bicarbonate excretion—

acidosis occurs as a side effect due to bicarbonate loss.

Side effect may also be based on a different facet of action, e.g. promethazine produces sedation which is unrelated to its antiallergic action; estrogens cause nausea which is unrelated to their antiovarulatory action.

An effect may be therapeutic in one context but side effect in another context, e.g. codeine used for cough produces constipation as a side effect but the latter is its therapeutic effect in traveller's diarrhoea; depression of A-V conduction is the desired effect of digoxin in atrial fibrillation, but the same may be undesirable when it is used for CHF.

Many drugs have been developed from observation of side effects, e.g. early sulfonamides used as antibacterial were found to produce hypoglycaemia and acidosis as side effects which directed research resulting in the development of hypoglycaemic sulfonylureas and carbonic anhydrase inhibitor—acetazolamide.

2. Secondary effects

These are indirect consequences of a primary action of the drug, e.g. suppression of bacterial flora by tetracyclines paves the way for superinfections; corticosteroids weaken host defence mechanisms so that latent tuberculosis gets activated.

3. Toxic effects

These are the result of excessive pharmacological action of the drug due to overdosage or prolonged use. Overdosage may be absolute (accidental, homicidal, suicidal) or relative (i.e. usual dose of gentamicin in presence of renal failure). The effects are predictable and dose related. They result from functional alteration (high dose of atropine causing delirium) or drug induced tissue damage (hepatic necrosis from paracetamol overdosage). The CNS, CVS, kidney, liver, lung, skin and blood forming organs are most commonly involved in drug toxicity.

Toxicity may result from extension of the therapeutic effect itself, e.g. coma by barbiturates, complete A-V block by digoxin, bleeding due to heparin.

Another action may be responsible for toxicity, e.g.—

Morphine (analgesic) causes respiratory failure in overdosage.

Imipramine (antidepressant) overdose causes cardiac arrhythmia.

Streptomycin (antitubercular) causes vestibular damage on prolonged use.

Poisoning Poisoning may result from large doses of drugs because 'it is the dose which distinguishes a drug from a poison'. Poison is a 'substance which endangers life by severely affecting one or more vital functions'. Not only drugs but other household and industrial chemicals, insecticides, etc. are frequently involved in poisonings. Specific antidotes such as receptor antagonists, chelating agents or specific antibodies are available for few poisons. General supportive and symptomatic treatment is all that can be done for others, and this is also important for poisons which have a selective antagonist.

These measures are:

1. *Resuscitation and maintenance of vital functions*

- Ensure patent airway, adequate ventilation, give artificial respiration/100% oxygen inhalation as needed.
- Maintain blood pressure and heart beat by fluid and crystalloid infusion, pressor agents, cardiac stimulants, etc, as needed.
- Maintain body temperature.
- Maintain blood sugar level by dextrose infusion, especially in patients with altered sensorium.

2. *Termination of exposure (decontamination)* by removing the patient to fresh air (for inhaled poisons), washing the skin and eyes (for poisons entering from the surface), induction of emesis with syrup ipecac or gastric lavage (for ingested poisons). Emesis should not be attempted in

comatose or haemodynamically unstable patient, as well as for kerosene poisoning due to risk of aspiration into lungs. These procedures are also contraindicated in corrosive and CNS stimulant poisoning. Emesis/gastric lavage is not recommended if the patient presents > 2 hours after ingesting the poison; if the poison/its dose ingested are known to be non life-threatening, or if the patient has vomited after consuming the poison.

3. *Prevention of absorption of ingested poisons*

A suspension of 20–40 g (1g/kg) of activated charcoal, which has large surface area and can adsorb many chemicals, should be administered in 200 ml of water. However, strong acids and alkalis, metallic salts, iodine, cyanide, caustics, alcohol, hydrocarbons and other organic solvents are not adsorbed by charcoal. Charcoal should not be administered if there is paralytic ileus or intestinal obstruction.

4. *Hastening elimination* of the poison by inducing diuresis (furosemide, mannitol) or altering urinary pH (alkalinization for acidic drugs, e.g. barbiturates). However, excretion of many poisons is not enhanced by forced diuresis and it is generally not employed now. Haemodialysis and haemoperfusion (passage of blood through a column of charcoal or adsorbant resin) are more efficacious procedures.

4. Intolerance

It is the appearance of characteristic toxic effects of a drug in an individual at therapeutic doses. It is the converse of tolerance and indicates a low threshold of the individual to the action of a drug. These are individuals who fall on the extreme left side of the Gaussian frequency distribution curve for sensitivity to the drug. Examples are:

- A single dose of triflupromazine induces muscular dystonias in some individuals, specially children.
- Only few doses of carbamazepine may cause ataxia in some people.
- One tablet of chloroquine may cause vomiting and abdominal pain in an occasional patient.

5. Idiosyncrasy

It is genetically determined abnormal reactivity to a chemical. The drug interacts with some unique feature of the individual, not found in majority of subjects, and produces the uncharacteristic reaction. As such, the type of reaction is restricted to individuals with a particular genotype (*see p. 64*). In addition, certain bizarre drug effects due to peculiarities of an individual (for which no definite genotype has been described) are included among idiosyncratic reactions, e.g.:

- Barbiturates cause excitement and mental confusion in some individuals.
- Quinine/quinidine cause cramps, diarrhoea, purpura, asthma and vascular collapse in some patients.
- Chloramphenicol produces nondose-related serious aplastic anaemia in rare individuals.

6. Drug allergy

It is an immunologically mediated reaction producing stereotype symptoms which are unrelated to the pharmacodynamic profile of the drug, generally occur even with much smaller doses and have a different time course of onset and duration. This is also called drug hypersensitivity; but does not refer to increased response which is called supersensitivity.

Allergic reactions occur only in a small proportion of the population exposed to the drug and cannot be produced in other individuals at any dose. Prior sensitization is needed and a latent period of at least 1–2 weeks is required after the first exposure. The drug or its metabolite acts as antigen (AG) or more commonly *hapten* (incomplete antigen: drugs have small molecules which become antigenic only after binding with an endogenous protein) and induce production of antibody (AB)/sensitized lymphocytes. Presence of AB to a drug is not necessarily followed by allergy to it. Chemically related drugs often show cross sensitivity. One drug can produce different types of allergic reactions in different individuals, while widely different drugs can produce the same reaction. The course of drug

allergy is variable; an individual previously sensitive to a drug may subsequently tolerate it without a reaction and *vice versa*.

Mechanism and types of allergic reactions

A. Humoral

Type-I (anaphylactic) reactions Reaginic antibodies (IgE) are produced which get fixed to the mast cells. On exposure to the drug, AG: AB reaction takes place on the mast cell surface (see Fig. 11.2) releasing mediators like histamine, 5-HT, leukotrienes especially LT-C₄ and D₄, prostaglandins, PAF, etc. resulting in urticaria, itching, angioedema, bronchospasm, rhinitis or anaphylactic shock. The manifestations occur quickly after challenge and are called *immediate hypersensitivity*. Antihistaminic drugs are beneficial in some of these reactions.

Type-II (cytolytic) reactions Drug + component of a specific tissue cell act as AG. The resulting antibodies (IgG, IgM) bind to the target cells; on reexposure AG: AB reaction takes place on the surface of these cells, complement is activated and cytolysis occurs, e.g. thrombocytopenia, agranulocytosis, aplastic anaemia, haemolysis, organ damage (liver, kidney, muscle), systemic lupus erythematosus.

Type-III (retarded, Arthus) reactions These are mediated by circulating antibodies (predominantly IgG, mopping AB). AG: AB complexes bind complement and precipitate on vascular endothelium giving rise to a destructive inflammatory response. Manifestations are rashes, serum sickness (fever, arthralgia, lymphadenopathy), polyarteritis nodosa, Stevens-Johnson syndrome (erythema multiforme, arthritis, nephritis, myocarditis, mental symptoms). The reaction usually subsides in 1–2 weeks.

B. Cell mediated

Type-IV (delayed hypersensitivity) reactions These are mediated through production of sensi-

tized T-lymphocytes carrying receptors for the AG. On contact with the AG these T cells produce *lymphokines* which attract granulocytes and generate an inflammatory response, e.g. contact dermatitis, some rashes, fever, photosensitization. The reaction generally takes > 12 hours to develop.

Treatment of drug allergy

The offending drug must be immediately stopped. Most mild reactions (like skin rashes) subside by themselves and do not require specific treatment. Antihistamines (H₁) are beneficial in some type I reactions (urticaria, rhinitis, swelling of lips, etc.) and some skin rashes (see p. 159). In case of anaphylactic shock or angioedema of larynx the resuscitation council of UK has recommended the following measures:

- Put the patient in reclining position, administer oxygen at high flow rate and perform cardiopulmonary resuscitation if required.
- Inject adrenaline 0.5 mg (0.5 ml of 1 in 1000 solution) i.m.; repeat every 5–10 min in case patient does not improve or improvement is transient. This is the only life saving measure. Adrenaline should not be injected i.v. (can itself be fatal) unless shock is immediately life threatening. If adrenaline is to be injected i.v., it should be diluted to 1:10,000 or 1:100,000 and infused slowly with constant monitoring.
- Administer a H₁ antihistaminic (chlorpheniramine 10–20 mg) i.m./slow i.v. It may have adjuvant value.
- Intravenous glucocorticoid (hydrocortisone sod. succinate 100–200 mg) should be added in severe/recurrent cases. It acts slowly, but is specially valuable for prolonged reactions and in asthmatics.

Adrenaline followed by a short course of glucocorticoids is indicated for bronchospasm attending drug hypersensitivity. Glucocorticoids are the only drug effective in type II, type III and type IV reactions.

Drugs frequently causing allergic reactions

Penicillins	Salicylates
Cephalosporins	Carbamazepine
Sulfonamides	Allopurinol
Tetracyclines	ACE inhibitors
Quinolones	Methyldopa
Antitubercular drugs	Hydralazine
Phenothiazines	Local anaesthetics

Skin tests (intradermal, patch) or intranasal tests may forewarn in case of Type I hypersensitivity, but not in case of other types. However, these tests are not entirely reliable—false positive and false negative results are not rare.

7. Photosensitivity

It is a cutaneous reaction resulting from drug induced sensitization of the skin to UV radiation. The reactions are of two types:

(a) Phototoxic Drug or its metabolite accumulates in the skin, absorbs light and undergoes a photochemical reaction followed by a photobiological reaction resulting in local tissue damage (sunburn-like), i.e. erythema, edema, blistering followed by hyperpigmentation and desquamation. The shorter wave lengths (290–320 nm, UV-B) are responsible. Drugs involved in acute phototoxic reactions are tetracyclines (especially demeclocycline) and tar products. Drugs causing chronic and low grade sensitization are nalidixic acid, fluoroquinolones, sulfones, sulfonamides, phenothiazines, thiazides, amiodarone. This type of reaction is more common than photoallergic reaction.

(b) Photoallergic Drug or its metabolite induces a cell mediated immune response which on exposure to light of longer wave lengths (320–400 nm, UV-A) produces a papular or eczematous contact dermatitis like picture. Rarely antibodies mediate photoallergy and the reaction takes the form of immediate flare and wheal on exposure to sun. Drugs involved are sulfonamides, sul-

fonylureas, griseofulvin, chloroquine, chlorpromazine.

8. Drug dependence

Drugs capable of altering mood and feelings are liable to repetitive use to derive euphoria, withdrawal from reality, social adjustment, etc. Drug dependence is a state in which use of drugs for personal satisfaction is accorded a higher priority than other basic needs, often in the face of known risks to health.

There is a lot of confusion in terminology and definitions; the following may serve to describe different aspects of the problem.

Psychological dependence It is said to have developed when the individual believes that optimal state of wellbeing is achieved only through the actions of the drug. It may start as liking for the drug effects and may progress to compulsive drug use in some individuals. The intensity of psychological dependence may vary from desire to craving. Obviously, certain degree of psychological dependence accompanies all patterns of self medication.

Reinforcement is the ability of the drug to produce effects that make the user wish to take it again or to induce *drug seeing behaviour*. Certain drugs (opioids, cocaine) are strong reinforcers, while others (benzodiazepines) are weak reinforcers. Faster the drug acts, more reinforcing it is.

Physical dependence It is an altered physiological state produced by repeated administration of a drug which necessitates the continued presence of the drug to maintain physiological equilibrium. Discontinuation of the drug results in a characteristic *withdrawal (abstinence) syndrome*. Since the essence of the process is adaptation of the nervous system to function normally in the presence of the drug, it has been called 'neuroadaptation'.

Drugs producing physical dependence are—opioids, barbiturates and other depressants including alcohol and benzodiazepines. Stimulant

drugs, e.g. amphetamines, cocaine produce little or no physical dependence.

Drug abuse Refers to use of a drug by self medication in a manner and amount that deviates from the approved medical and social patterns in a given culture at a given time. The term conveys social disapproval of the manner and purpose of drug use. For regulatory agencies, *drug abuse* refers to any use of an illicit drug.

Drug addiction It is a pattern of compulsive drug use characterized by overwhelming involvement with the use of a drug. Procuring the drug and using it takes precedence over other activities. Even after withdrawal most addicts tend to relapse. Physical dependence, though a strong impetus for continued drug use, is not an essential feature of addiction. Amphetamines, cocaine, cannabis, LSD are drugs which produce addiction but little/no physical dependence. On the other hand, drugs like nalorphine produce physical dependence without imparting addiction in the sense that there is little drug seeking behaviour.

Drug habituation It denotes less intensive involvement with the drug, so that its withdrawal produces only mild discomfort. Consumption of tea, coffee, tobacco, social drinking are regarded habituating, physical dependence is absent.

Basically, habituation and addiction imply different degrees of psychological dependence and it may be difficult to draw a clearcut line of distinction between the two. Therefore, it is better to avoid using these terms in describing drug dependence and related conditions.

9. Drug withdrawal reactions

Apart from drugs that are usually recognised as producing dependence, sudden interruption of therapy with certain other drugs also results in adverse consequences, mostly in the form of worsening of the clinical condition for which the drug was being used, e.g.:

- (i) Acute adrenal insufficiency may be precipitated by abrupt cessation of corticosteroid therapy.

- (ii) Severe hypertension, restlessness and sympathetic overactivity may occur shortly after discontinuing clonidine.
- (iii) Worsening of angina pectoris, precipitation of myocardial infarction may result from stoppage of β blockers.
- (iv) Frequency of seizures may increase on sudden withdrawal of an antiepileptic.

These manifestations are also due to adaptive changes and can be minimized by gradual withdrawal.

10. Teratogenicity

It refers to capacity of a drug to cause foetal abnormalities when administered to the pregnant mother. The placenta does not strictly constitute a barrier and any drug can cross it to a greater or lesser extent. The embryo is one of the most dynamic biological systems and in contrast to adults, drug effects are often irreversible. The thalidomide disaster (1958–61) resulting in thousands of babies born with *phocomelia* (seal like limbs) and other defects focused attention to this type of adverse effect.

Drugs can affect the foetus at 3 stages—

- (i) *Fertilization and implantation*—conception to 17 days—failure of pregnancy which often goes unnoticed.
- (ii) *Organogenesis*—18 to 55 days of gestation—most vulnerable period, deformities are produced.
- (iii) *Growth and development*—56 days onwards—developmental and functional abnormalities can occur, e.g. ACE inhibitors can cause hypoplasia of organs, specially lungs and kidneys; NSAIDs may induce premature closure of ductus arteriosus.

The type of malformation depends on the drug as well as the stage of exposure to the teratogen. Foetal exposure depends on the blood level and duration for which the drug remains in maternal circulation. The teratogenic potential of a drug is to be considered against the background of congenital abnormalities occurring spontaneously,

Human teratogenic drugs	
Drug	Abnormality
Thalidomide	phocomelia, multiple defects
Anticancer drugs (methotrexate)	cleft palate, hydrocephalus, multiple defects, foetal death
Androgens	virilization; limb, esophageal, cardiac defects
Progestins	virilization of female foetus
Stilboestrol	vaginal carcinoma in teenage female offspring
Tetracyclines	discoloured and deformed teeth, retarded bone growth
Warfarin	depressed nose; eye and hand defects, growth retardation
Phenytoin	hypoplastic phalanges, cleft lip/palate, microcephaly
Phenobarbitone	various malformations
Carbamazepine	neural tube defects, other abnormalities
Valproate sod.	spina bifida and other neural tube defects
Alcohol	low IQ baby, growth retardation, foetal alcohol syndrome
ACE inhibitors	hypoplasia of organs, growth retardation, foetal loss
Lithium	foetal goiter, cardiac and other abnormalities
Antithyroid drugs	foetal goiter and hypothyroidism
Indomethacin/aspirin	premature closure of ductus arteriosus
Isotretinoin	craniofacial, heart and CNS defects

Risk category of drugs during pregnancy		
Category		Examples
A	Adequate studies in pregnant women have failed to demonstrate a risk to the foetus	Inj. Mag. sulfate, thyroxine
B	Adequate human studies are lacking, but animal studies have failed to demonstrate a risk to the foetus or Adequate studies in pregnant women have failed to demonstrate a risk to the foetus, but animal studies have shown an adverse effect on the foetus	Penicillin V, amoxicillin, cefactor, erythromycin, paracetamol, lignocaine
C	No adequate studies in pregnant women and animal studies are lacking or have shown and adverse effect on foetus, but potential benefit may warrant use of the drug in pregnant women despite potential risk	Morphine, codeine, atropine, corticosteroids, adrenaline, thiopentone, bupivacaine
D	There is evidence of human foetal risk, but the potential benefits from use of the drug may be acceptable despite the potential risk	Aspirin, phenytoin, carbamazepine, valproate, lorazepam
X	Studies in animals or humans have demonstrated foetal abnormalities, and potential risk clearly outweighs possible benefit	Estrogens, isotretinoin, ergometrine

which is ~ 2% of all pregnancies. Majority of implicated drugs are low grade teratogens, i.e. increase the incidence of malformations only slightly, which may be very difficult to detect, confirm or refute. Nevertheless, some drugs have been clearly associated with causing foetal abnormalities in human beings. These are listed in the box. However, only few mothers out of those who receive these drugs during the vulnerable period will get a deformed baby, but the exact risk posed by a drug is difficult to estimate.

The US-FDA has graded the documentation of risk for causing birth defects into five categories (see box).

It is, therefore, wise to avoid all drugs during pregnancy unless compelling reasons exist for their use regardless of the assigned pregnancy category, or presumed safety (also See Appendix-2).

Frequency of spontaneous as well as drug induced malformations, especially neural tube defects, may be reduced by folate therapy during pregnancy.

11. Mutagenicity and Carcinogenicity

It refers to capacity of a drug to cause genetic defects and cancer respectively. Usually oxidation of the drug results in the production of reactive intermediates which affect genes and may cause structural changes in the chromosomes. Covalent

interaction with DNA can modify it to induce mutations, which may manifest as heritable defects in the next generation. If the modified DNA sequences code for factors that regulate cell proliferation/growth, i.e. are protooncogenes, or for proteins that inhibit transcription of protooncogenes, a tumour (cancer) may be produced. Even without interacting directly with DNA, certain chemicals can promote malignant change in genetically damaged cells, resulting in carcinogenesis. Chemical carcinogenesis generally takes several (10–40) years to develop. Drugs implicated in these adverse effects are—anticancer drugs, radioisotopes, estrogens, tobacco. Generally, drugs which show mutagenic or carcinogenic potential are not approved for marketing/are withdrawn, unless useful in life-threatening conditions.

12. Drug induced diseases

These are also called *iatrogenic* (physician induced) diseases, and are functional disturbances (disease) caused by drugs which persist even after the offending drug has been withdrawn and largely eliminated, e.g.:

- Peptic ulcer by salicylates and corticosteroids.
- Parkinsonism by phenothiazines and other antipsychotics.
- Hepatitis by isoniazid.
- DLE by hydralazine.