Pharmacovigilance : Concepts, Applications and Current Scenario

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Vice – Chancellor

NIMS University, Jaipur



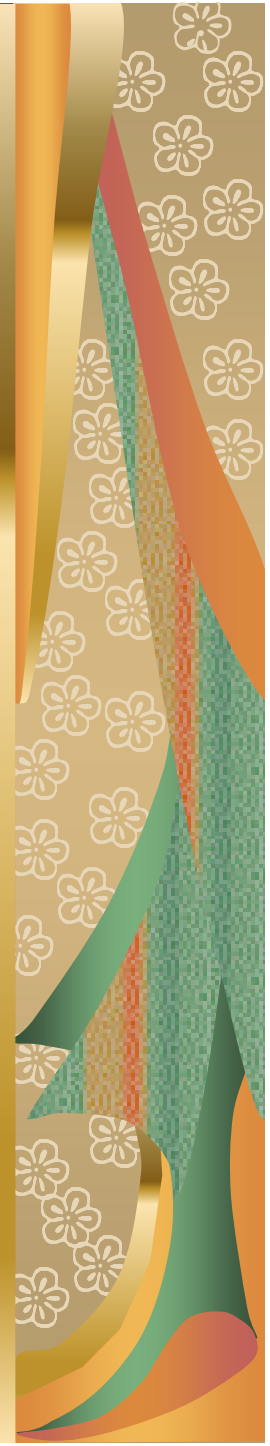
Worrying Experiences

1946 Streptomycin Deafness, Renal failure

1958 Isoniazid Hepatitis

1952 Chloramphenicol Aplastic anaemia

1961 Thalidomide – Phocomelia (prenatal exposure)



1964 Phenylbutozone – Aplastic Anaemia

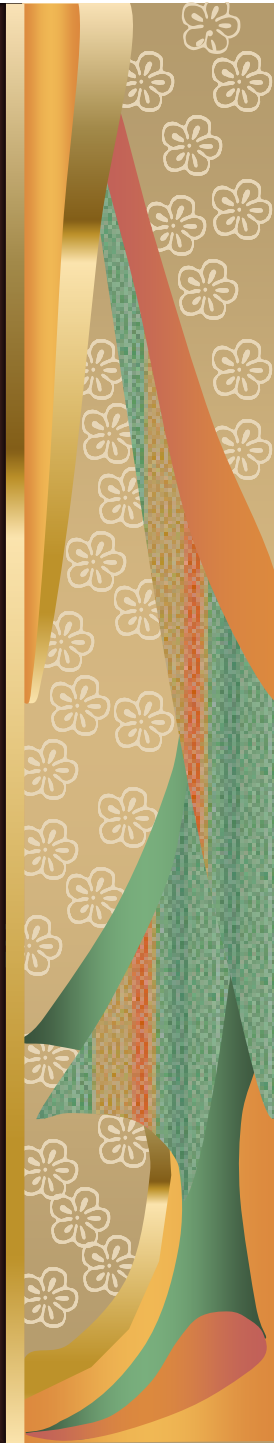
1965 Agranulocytosis

1966 Aspirin + NSAIDS – GI ulcer bleeding

1966 Oral contraceptive – Thromboembolic disease

1970 Clioquinol – SMON

1974 Practolol – Oculomucocutaneous Syndrome



1982 Ketaconozole – Hepatitis

1984 Valproate sodium – Spina bifida

1986 Ofloxacin – Psychosis

1988 Ceftriaxone – Biliary lithiasis

1994 Fluroquinolones – Achilis Tendinitis & rupture

1997 Indinavir – Haemolytic anaemia

2001 Nemusalide – Hepatitis









CATASTROPHIC THALIDOMIDE











Birth Defects

For those babies who survived, birth defects included:

- *Deafness*
- *Blindness*
- *Disfigurement*
- *Cleft palate*
- *Internal disabilities*
- *Phocomelia (most affected)*



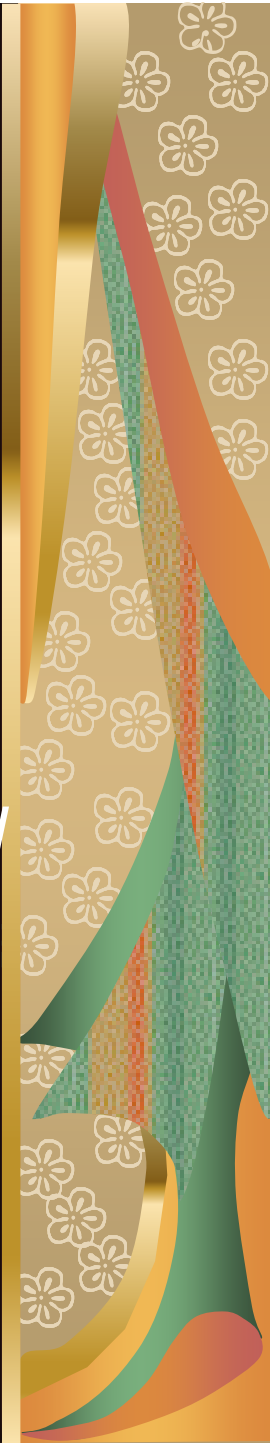
History of Pharmacovigilance

1948 *starts collecting side effects after a death caused by anesthesia*

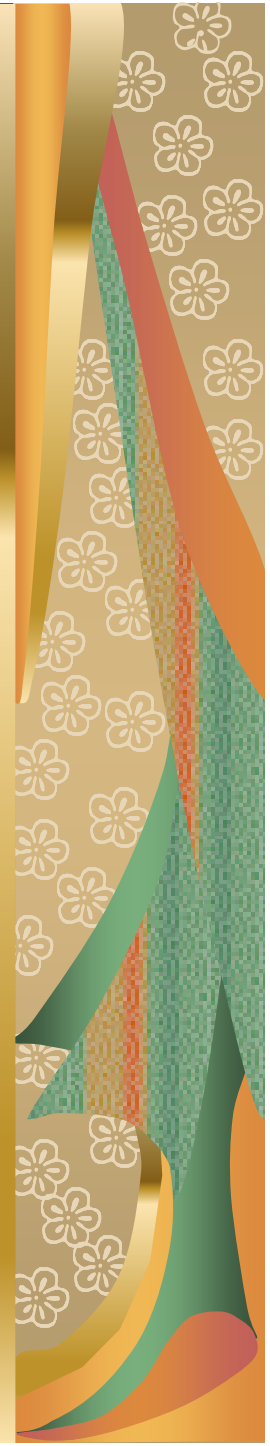
1906- ***US*** *federal food and Drug Act Pharmaceuticals be pure and free from Contamination.*

1937- USA *107 lethal cases after diethylenglycol was mistakenly used to solubilize sulphonamides.*

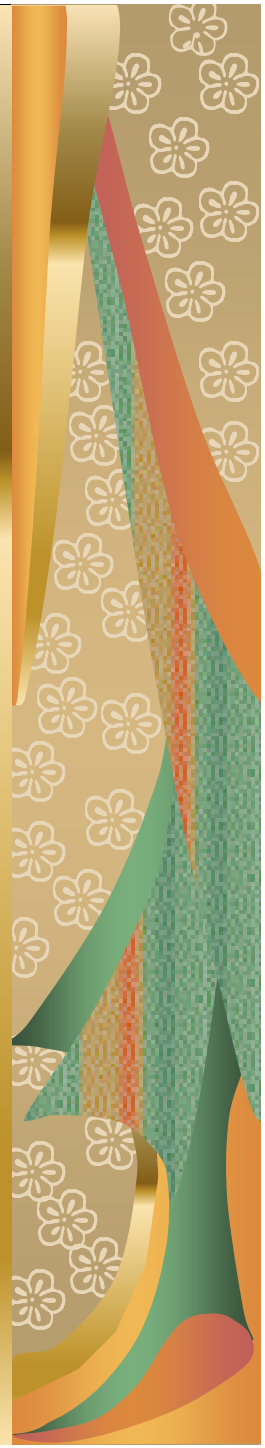
1952- France *100 lethal cases after diethyl tin diodide was mistakenly used in a skin preparation.*



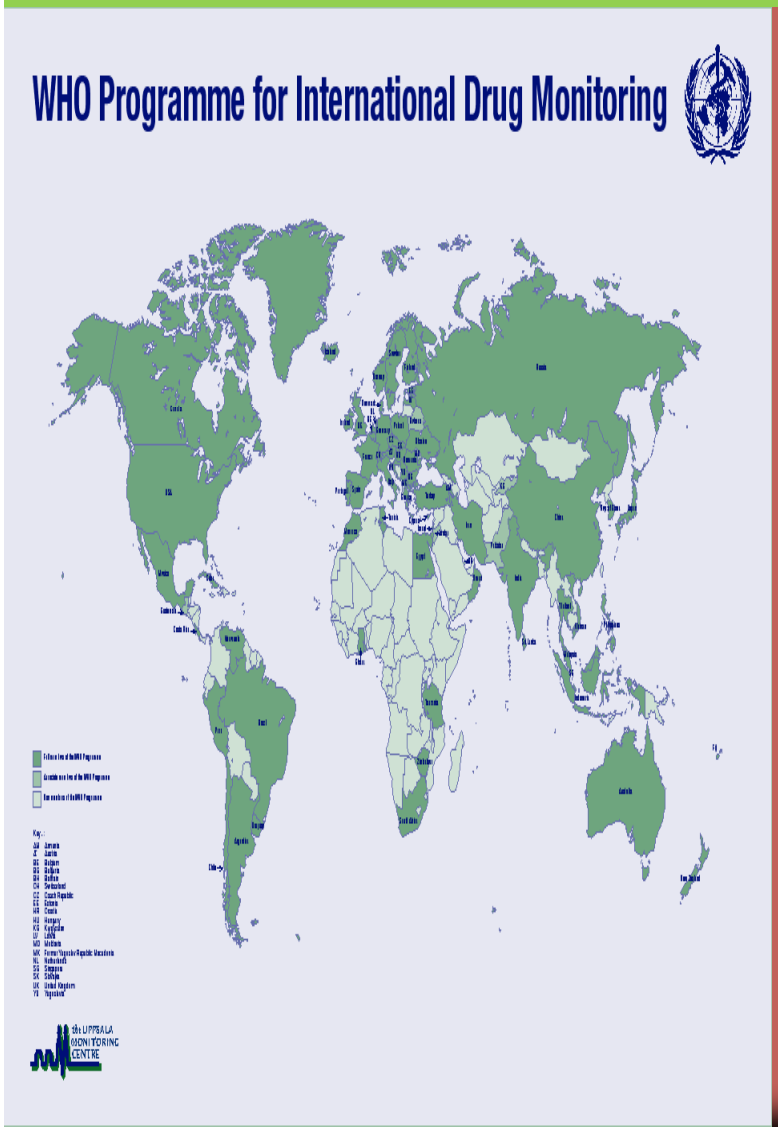
1959-61	Thalidomide – sleep inducing drug
1962 USA	prove safety and efficacy before Marketing
1964	UK yellow card system
1967	WHO's international Drug Monitoring programme.



- Animal Tests do not predict Absolute safety
  Thalidomide was safe in pregnant rats.
- With proper safety measures even dangerous drugs could be valuable.
- (Thalidomide now used in leprosy Type II reactions erythema nodosum leprosum.
- Safety measures cannot be followed 100% (In some countries with use of Thalidomide for Leprosy new Thalidomide children have been reported.
- Lesson from Thalidomide catostrophy



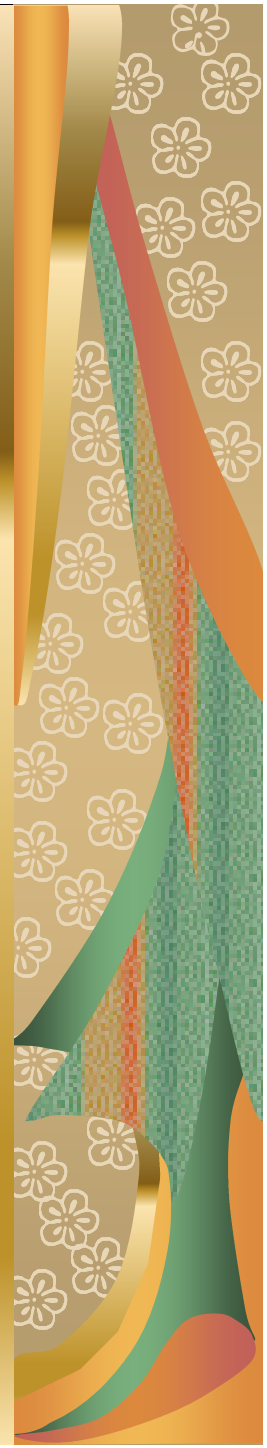
Pharmacovigilance



WHO 2002

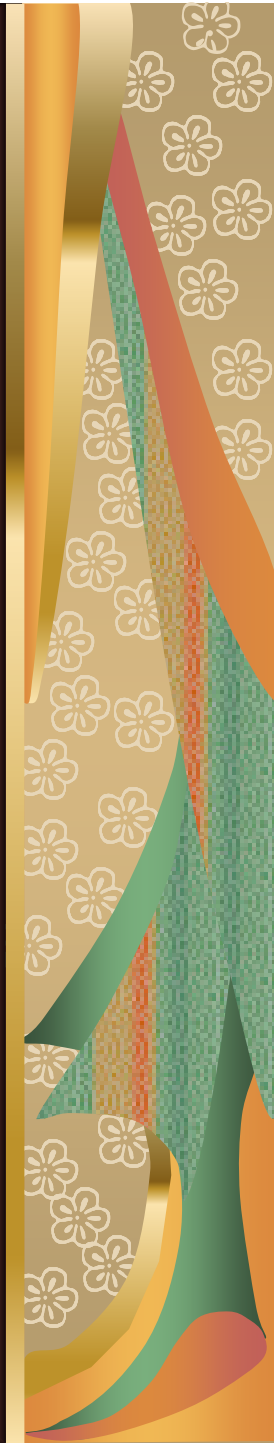
Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of Adverse effects or any other drugs related

Causality Assessment



Causality assessment

- Patient
- Treating physician
- ADR monitoring center
- Drug manufacturer
- Drug control authority



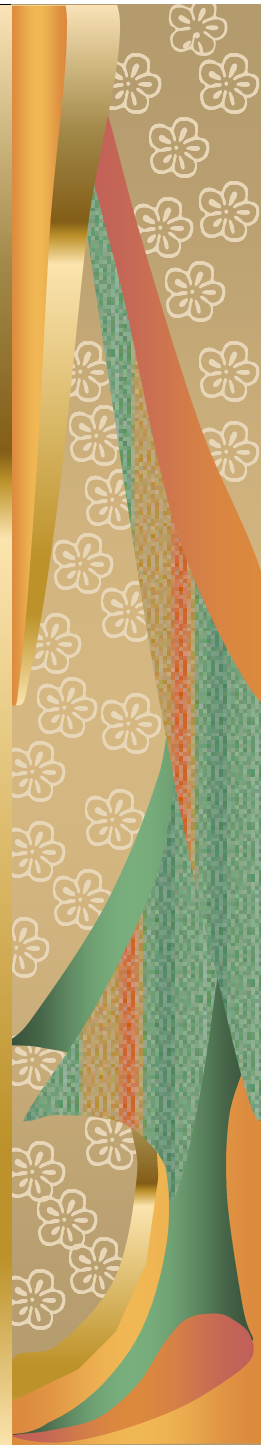
Causality assessment

- **Three Key Questions**

  * **Can the drug cause adverse reaction**

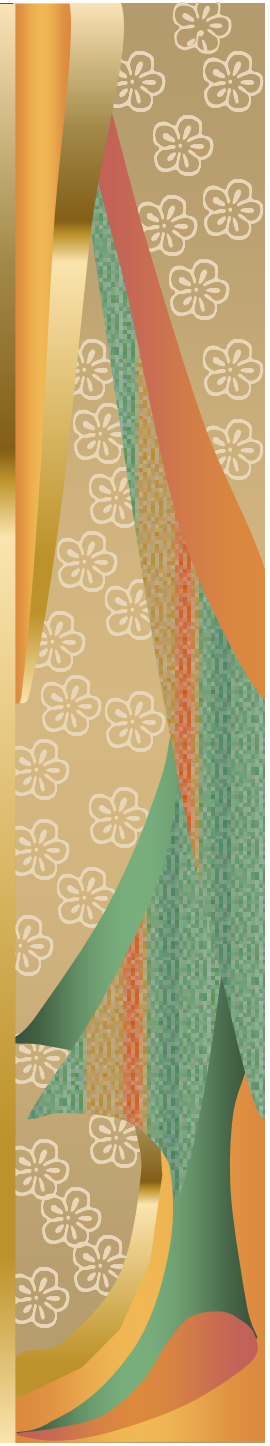
  * **Has the drug caused the adverse reaction**

  * **Will the drug cause the adverse reaction**



Causality assessment Making a differential diagnosis

How likely is that this medication is the cause of this problem in this particular patient

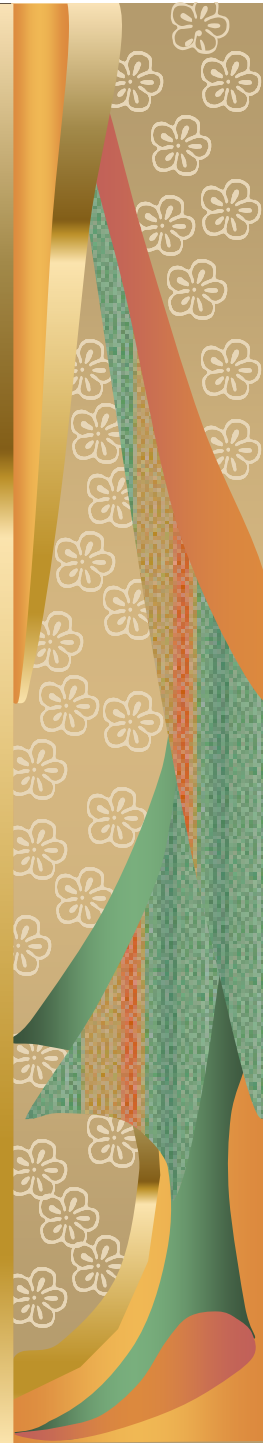


Approach to causality assessment

* individual expert

* panel of experts

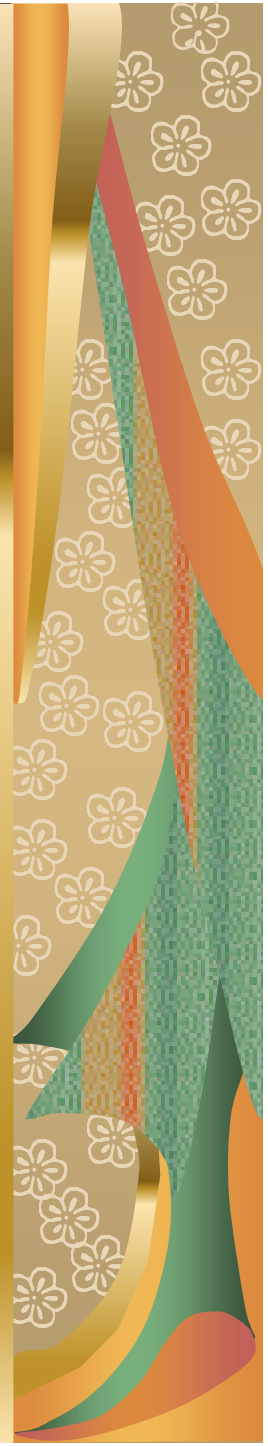
* formal algorithm
  - decrease inter-individual differences
  - improve validity
  - time consuming



Causality assessment

* **First step**

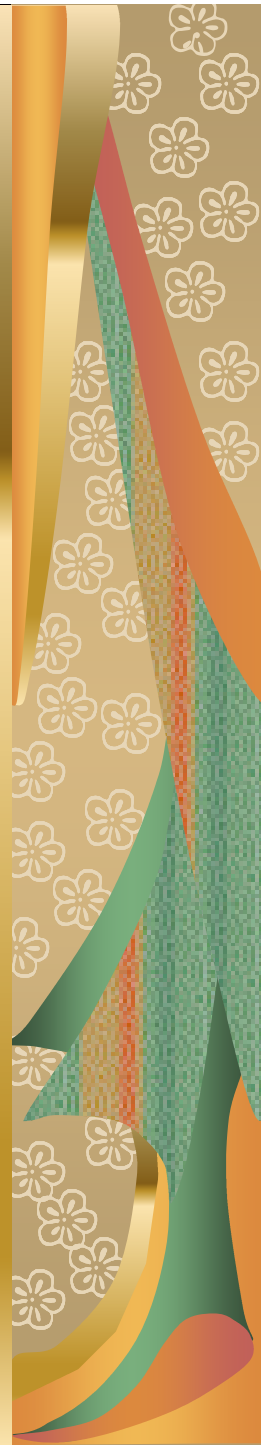
  - **Make sure you have access to all available details**



Data elements relevant to causality assessment

- Age , sex and medical history
- Identified suspected and other drugs,
  routes, start stop dates and indications for use
- Description of adverse event, including clinical data,
  laboratory results and date of onset (or interval)

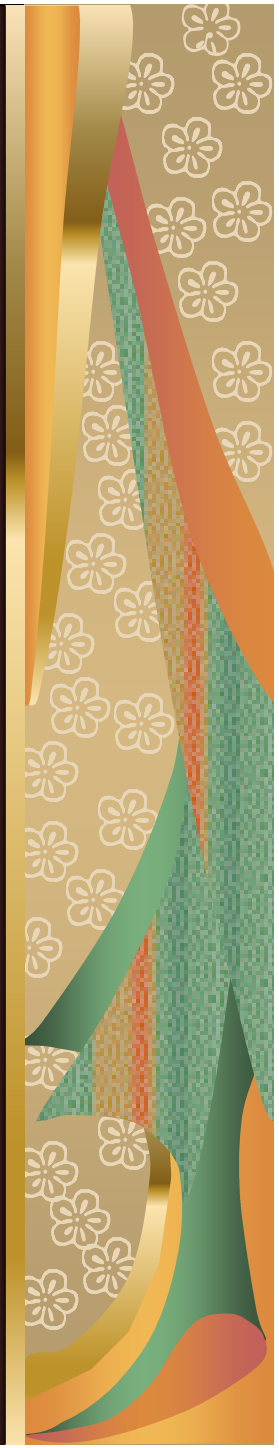
* Treatment course and outcome



Four assessment criteria

- The association in time (place) between drug administration and event
- Pharmacology (features, previous knowledge of side effects)
- Medical plausibility (characteristic signs and symptoms, laboratory tests, pathological findings)

* Likelihood or exclusion of other causes



Causality assessment

Main factors to consider

Reasonable time relationship

*** pharmacokinetics**

*** type of reaction**

Site of action

Dose response

*** effect of dose reduction**

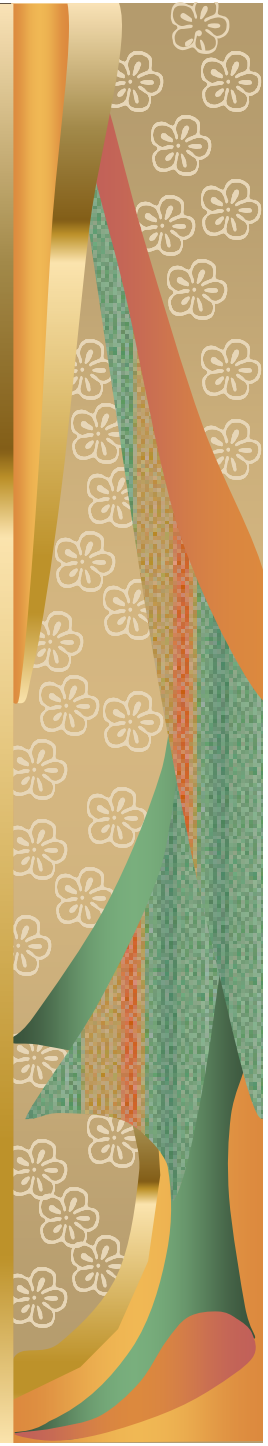
*** effect of re-exposure**

Known actions of drug

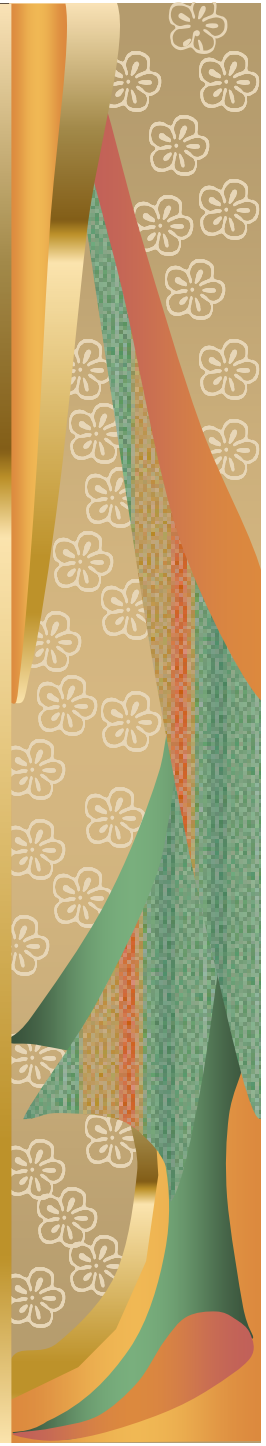
Other drugs taken

*** traditional remedies**

Effects of underlying disease or conditions



Essential elements required in an adverse reaction report



1 2 3 4 5 6

James while sleeping on a bank was flattened by a arjun

7 8 9

tank the ground was soft the tank was large and james was

10 11

Buried free of Charge

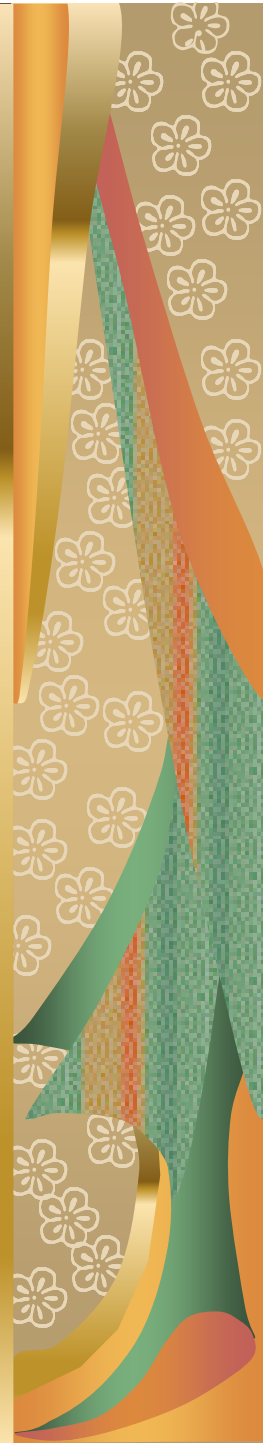
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1. Patient Identity 2. Timing 3. Disease 4. Place

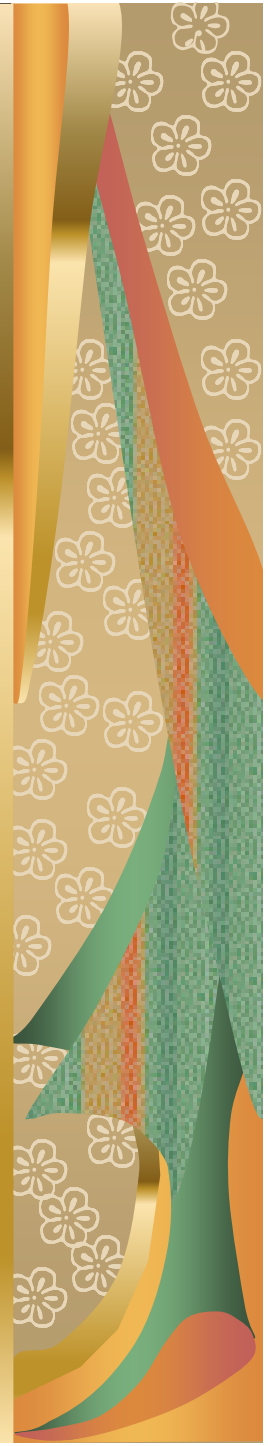
5. adverse effect 6. Drug (Propritary) 7. Drug name approved

8. Predisposing factors 9. Dose 10. Direct consequence

11. Indirect consequence

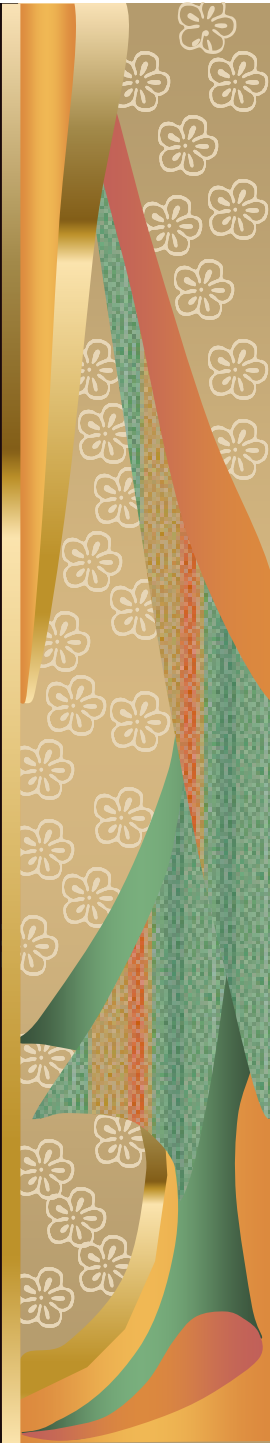


Medical Errors



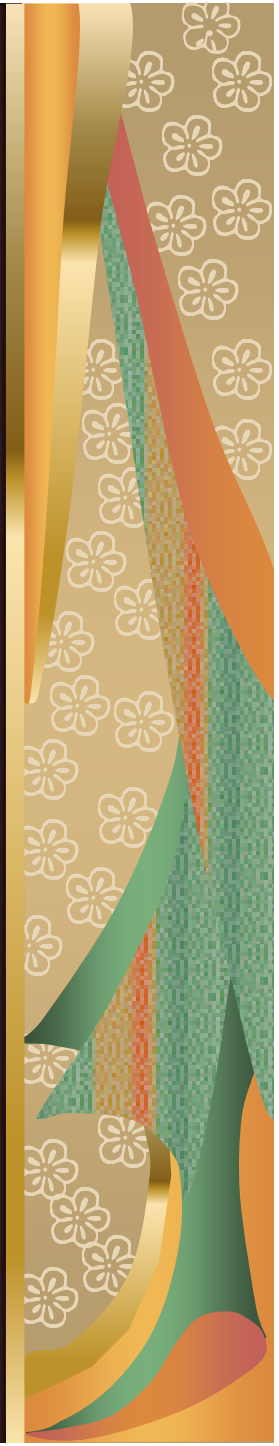
Error

Error is defined as the failure of a planned action to be completed as intended (i.e **error of execution**) or the use of the wrong plan to achieve an aim (e.g. **error of planning**).



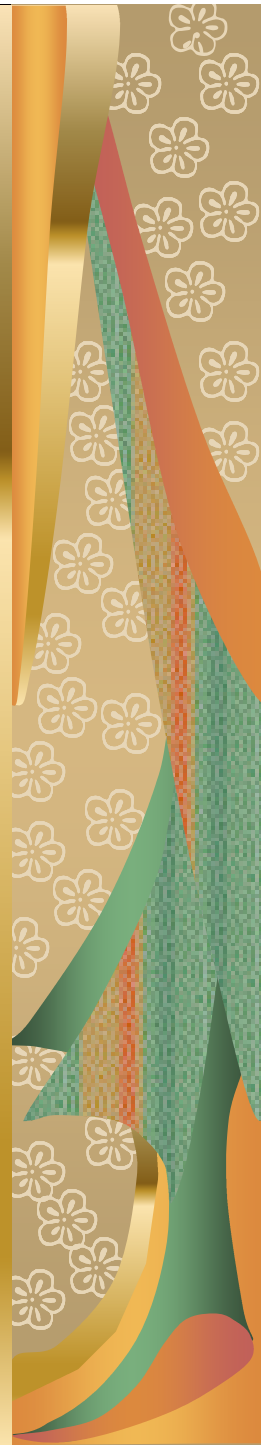
What to do ?

Human beings in all walks of life commit errors and so also in the field of Medicare. These errors not only result in morbidity in a significant proportion of population but even lead to mortality. Most of these errors are preventable by designing a system that make it hard for people to commit errors



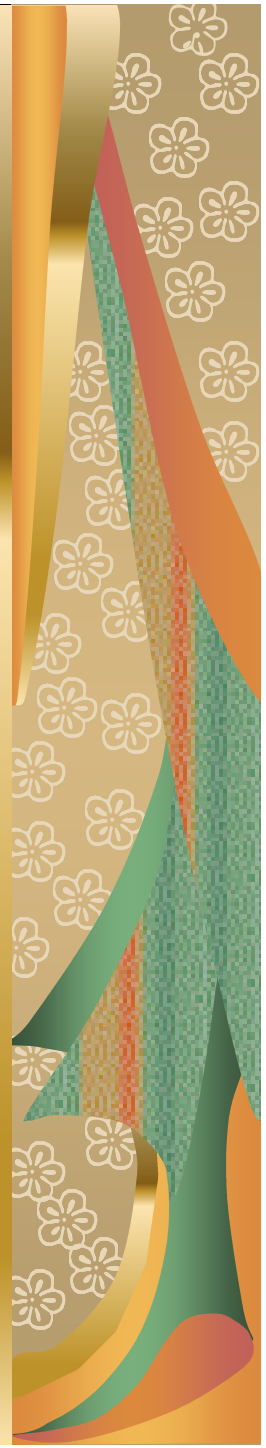
Tip of the iceberg

- *When we hear of or read in news papers about wrong eye operated ,*
- *wrong leg amputated,*
- *anaesthetist strayed out of operation theatre and patient went into coma due to overdosage of anaesthetic agent,*
- *wrong drug administered and so on, these are just*



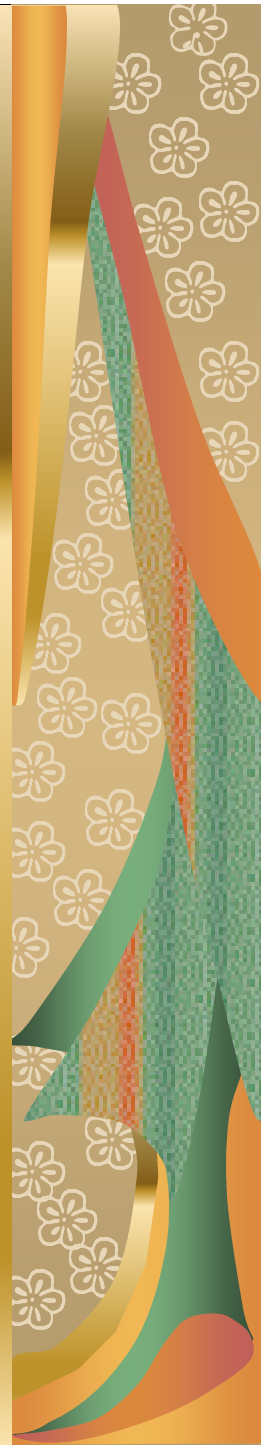
Situation in India

- The incidence of deaths as a result of medical errors in India is any bodies guess as no prospective or retrospective study on this issue is available.
- However, even by a conservative estimate the risk of dying as a result of medical error far surpasses the risk of dying in a road accident



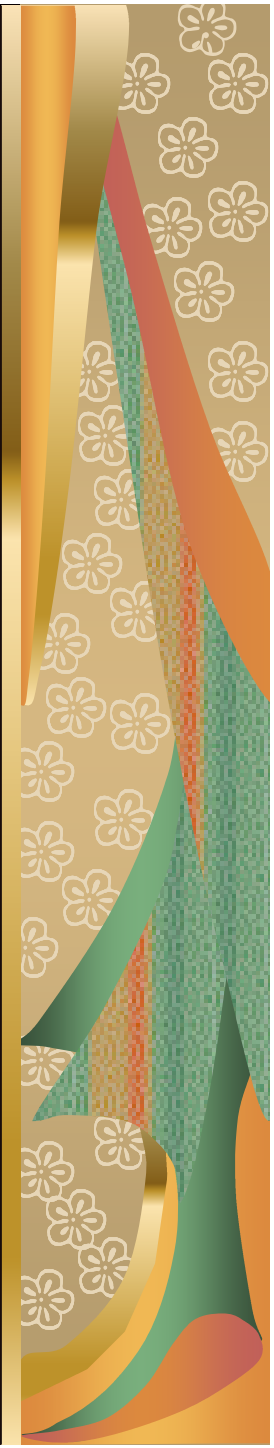
Legal Protection against error

- To error is human.
- A physician or health care provider can not be held responsible for each and every harm caused to the patient as a result of the institution of therapy.
- physician is not the sole or single entity which can be held responsible for the outcome of therapy.
- Biological variations, pathological state, quality of drugs, Adverse drug reactions, failure on the part of pharmacist or nurse, investigating agencies (Pathologist, radiologist etc) failure to follow the instructions by the patient by himself or on the advice of friends relatives
- God's will which determine the course of disease and its outcome.



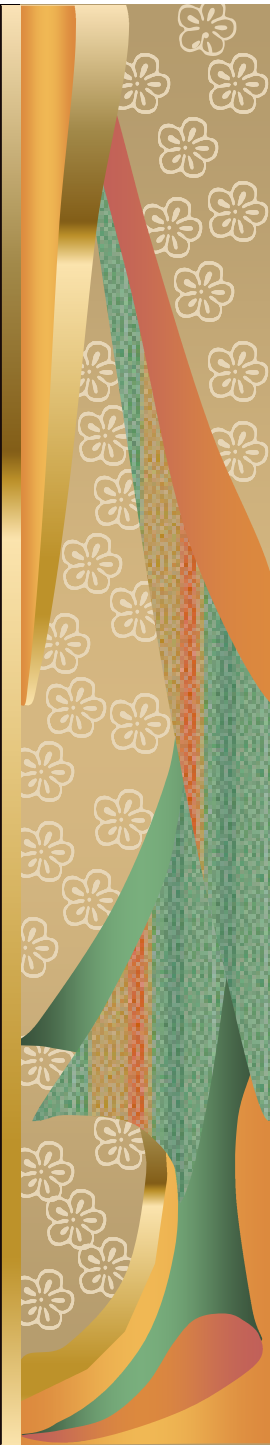
Limitations of clinical trial for safety assessment

Too few patients	Average 1500 patients
Too simple	Only patients without medical complications
Too median aged	Not children , not old
Too narrow	Only well-defined
specific	indications
Too brief	Exposure & observation



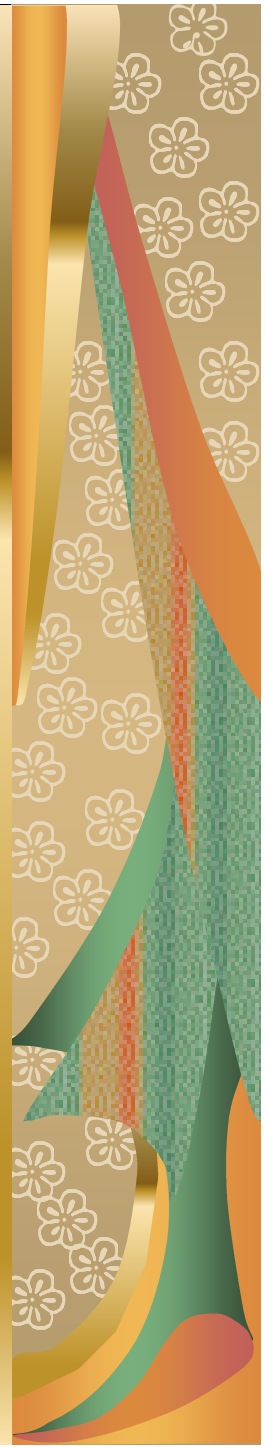
ADR monitoring sample size

Incidence of ADR	no. required
1:10	200
1:100	2,300
1:1000	23,000



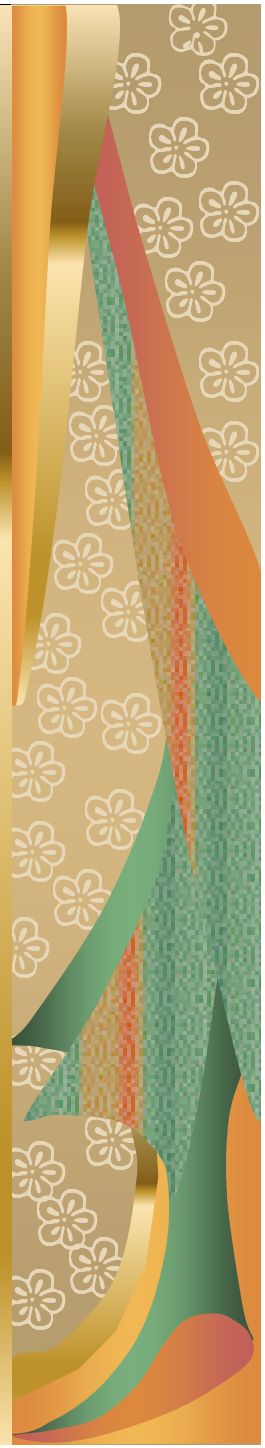
Risk Levels – CIOMS

- **Very common** > 1 in exposures
- **Common** < 1 in 10 but > 1 in 100
- **Uncommon** < 1 in 100 but > 1 in1000
- **Rare** < 1 in 1000 but >1 in 10000
- **Very rare** < 1 in 10000



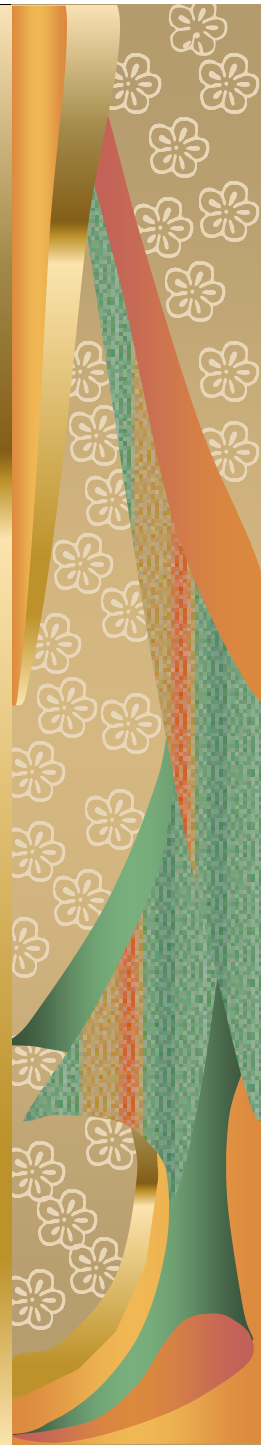
Delay in identifying ADRs – some examples

Drug	ADR	Years after use
Amidopyrin	BMD	47
Cinchophen	Jaundice	15
Chloramphenicol	Aplastic anaemia	20
Aspirin	Gastric haemorrhage	39
Clioquinol	SMON	35
Diethylstiblbestrol	Adenocarcinoma cervix, vagina	20
Practolol	Oculomucocutaneous syndrome	5



Classification of ADR

- A - Augmented Pharmacological response
- B - Bizarre - Hypersensitivity reactions
- C - Continuous
- D - Delayed
- E - Ending of use
- F - Failure of treatment



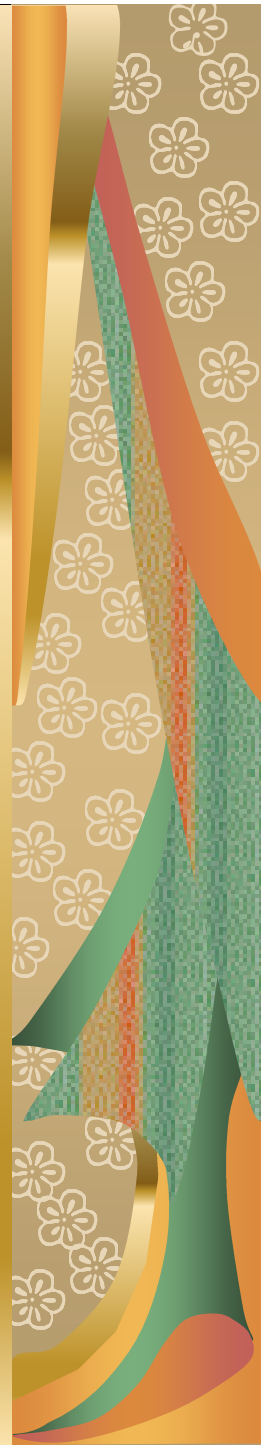
Adverse Reaction Type A

- *Reaction caused by normal but enhanced*

  Pharmacological effects of a drug given in therapeutic doses.

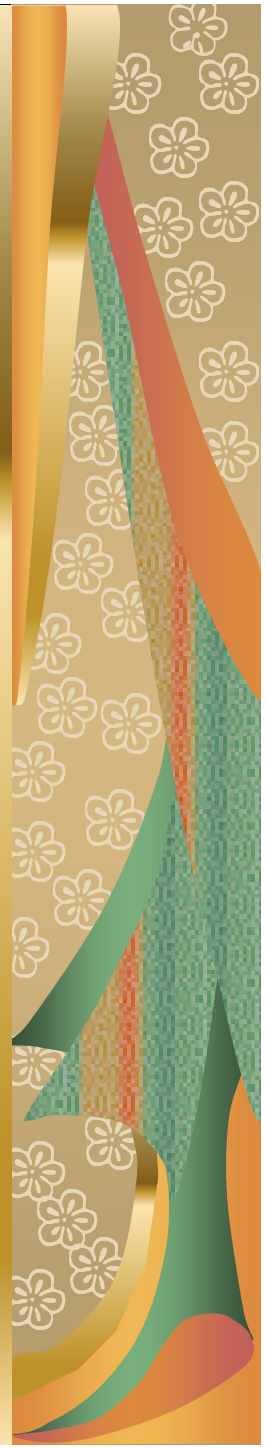
- *Reaction caused by physical and / or chemical*

  properties of the drugs.



Adverse Reactions Type B

- ***Bizarre and unpredictable***
- ***Dose relationship not obvious***
- ***Often of allergic origin***



Types of ADRs

A

75%



B

25%

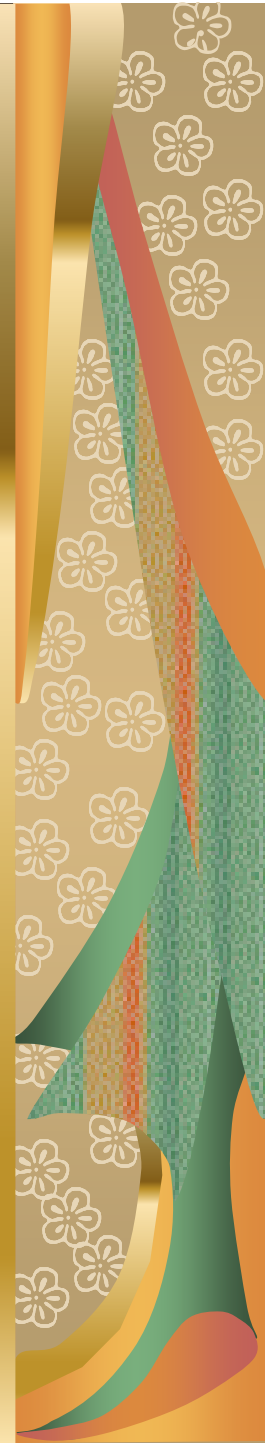


Most important approach for a patient's welfare programme is good teaching in clinical pharmacology and therapeutics at undergraduate and postgraduate level

Adverse Drug Reactions

Causes of Type A

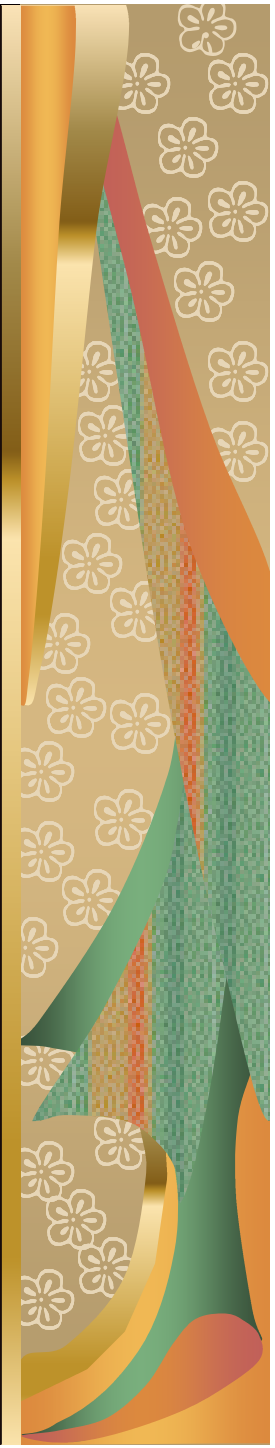
1. *Pharmacokinetic*
2. *Pharmacodynamic*
3. *Dose-dependent*



Type B adverse effects

Patient reactions

- Immuno-allergic reactions
- Metabolic intolerance (e.g. inborn errors)
- Idiosyncrasy
    - * Rare (< 1 %), unexpected
    - * Causality uncertain
    - * Mechanism uncertain
    - * No dose relationship
    - * Not reproducible
    - * Characteristic, serious
    - * Suggestive time relationship
    - * Low background frequency

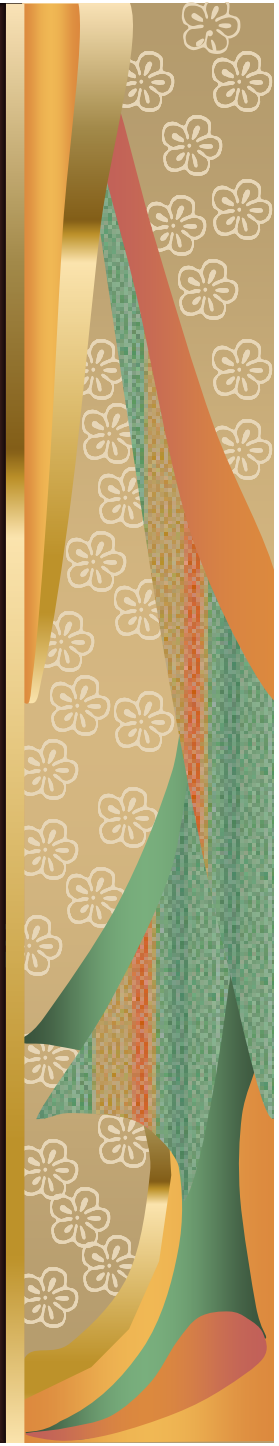


Type B
Allergic Reactions

According to Coomb and Gell 1975

Type I	Anaphylactic
Type II	Cytotoxic
Type III	Immune complex mediated
Type IV	Cell mediated

In real life one drug (even in the single patient) can cause
reactions by different mechanisms.

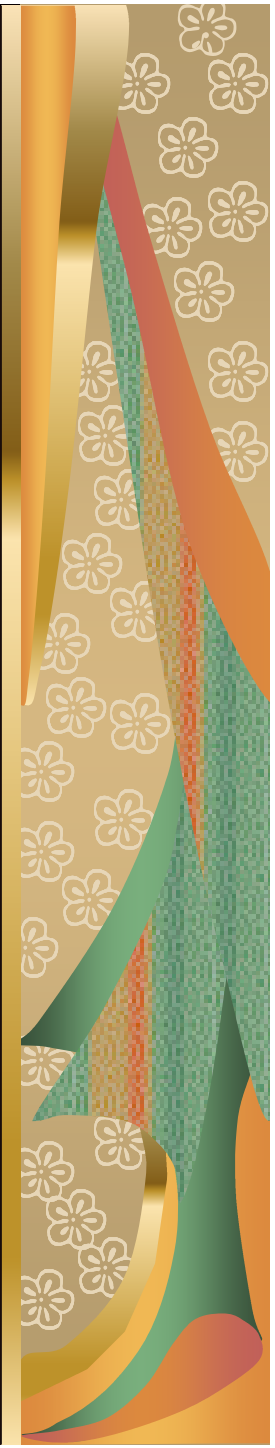


Characteristics of

Allergic reactions

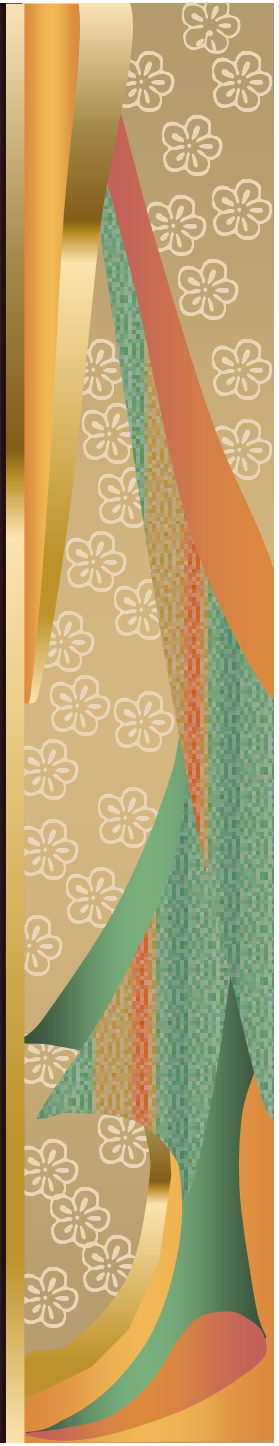
- Delay initial exposure – allergy established
- Allergy precipitated by minute amounts
- Recurrence on repeated exposure
- Reaction do not resemble pharmacological activity
- Symptoms suggestive; urticaria serum sickness,

  anaphylaxis etc.



Characteristics of ADRs

	Type A (Augmented response attenuated response)	Type B (Bizarre)
Predictable Pharmacologically	Yes	No
Dose dependent	Yes	No
Incidence and Morbidity	High	Low
Mortality	Low	High
Treatment	Change dose	Stop



Pharmacovigilance in India
Attempt 1st

1st April 1989 sponsored by ICMR 6 centres at Medical colleges .

JNMC Aligarh

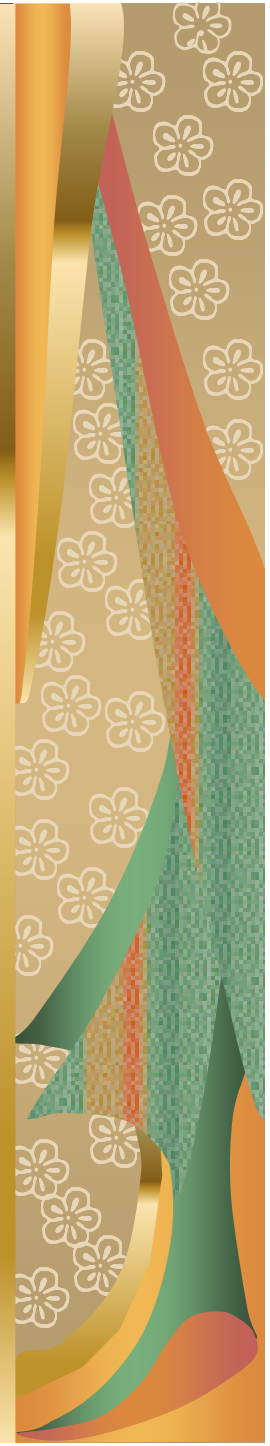
MLBMC Jhansi

AIIMS New Delhi

MAMC New Delhi

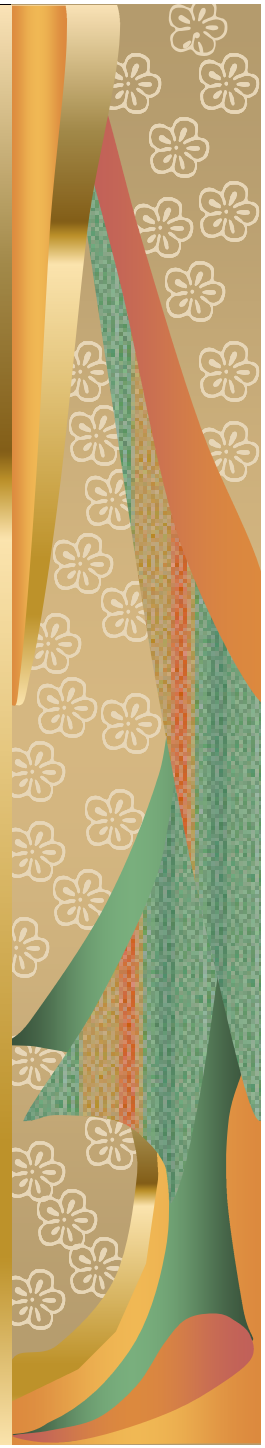
LLRMC Meerut

CMC Vellore.



Pharmacovigilance in India

- *2nd Multi centric study 12 centres sponcered.*
- *JNMC Aligarh,*
- *LTMC Mumbai,*
- *Govt MC Jammu,*
- *Medical College Baroda,*
- *Medical College Guwahati,*
- *Chennai MC Chennai,*
- *GMC Bhopal,*
- *Osmania MC Hyderabad,*
- *MAMC New Delhi*
- *CMC Vellore,*
- *St. John's Bangalore,*
- *Medical Thiruvanantpuram*



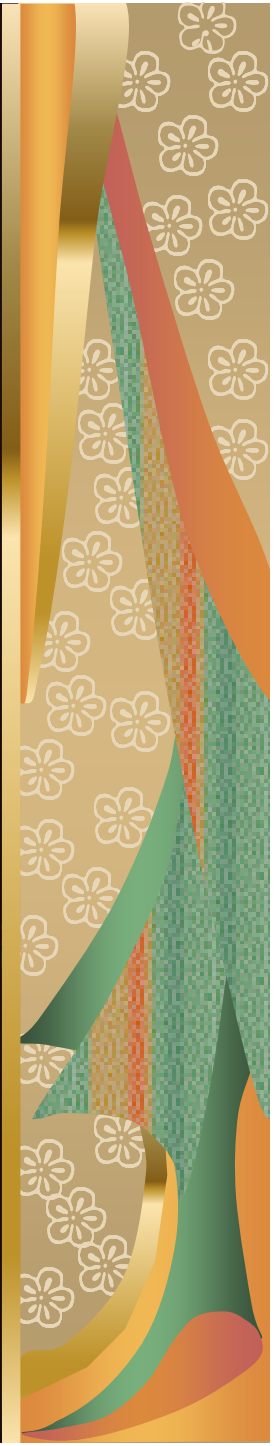
National Pharmacovigilance Program CDSCO

January 2005 (Financed by WHO)

Foster reporting culture

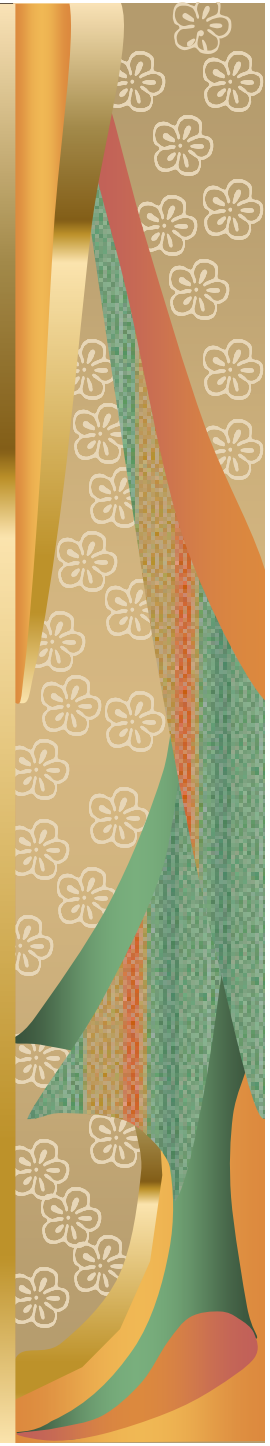
Involve Healthcare Professionals

Bench mark for global drug monitoring



WHO special centres for ADR Monitoring

1. *J.N.Medical College, AMU, Aligarh.*
2. *KEM college* **Mumbai.**




THANK YOU