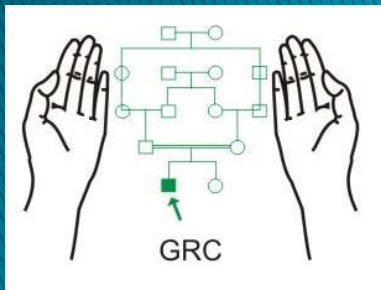


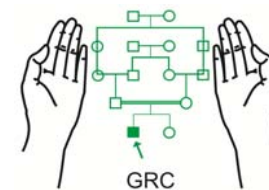
# Research Designs

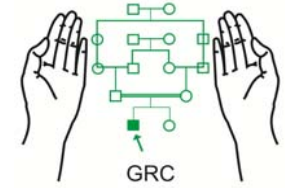
Maj Gen (R) Suhaib Ahmed, HI (M)  
MBBS; MCPS; FCPS; PhD (London)

Genetics Resource Centre (GRC)



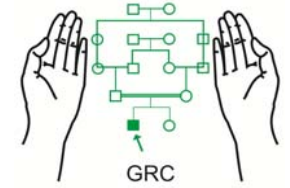
[www.grcpk.com](http://www.grcpk.com)





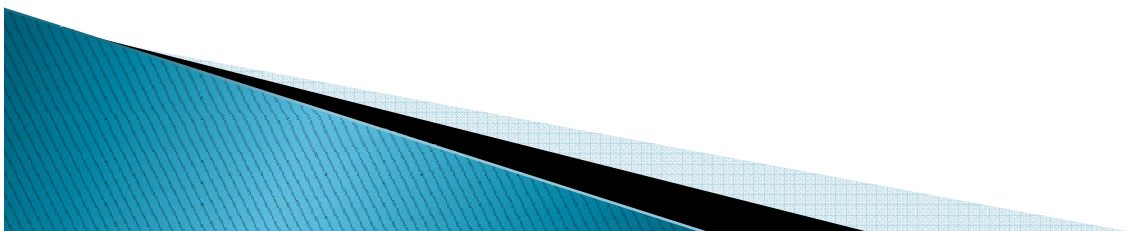
- ▶ Probably no aspect of clinical research is as neglected as study design. Eager young investigators attend classes on medical statistics, find dozens of ways to compute “ $P$ ” values, but rarely learn how to organize a clinical research project.
- ▶ Yet careful study design is the foundation of quality clinical research.

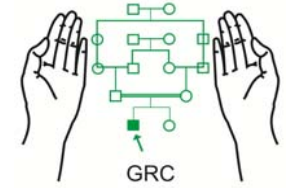
(Noller & Melton, 1985)



There are only handful of ways to do a study properly but a thousand ways to do it wrong

(Sackett, 1986)





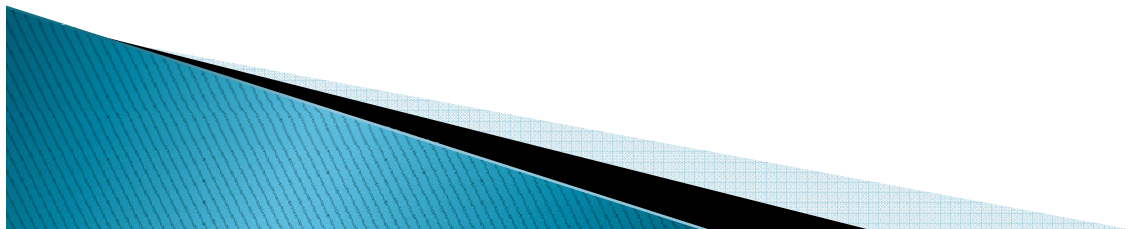
# Research Designs

## ► Observational

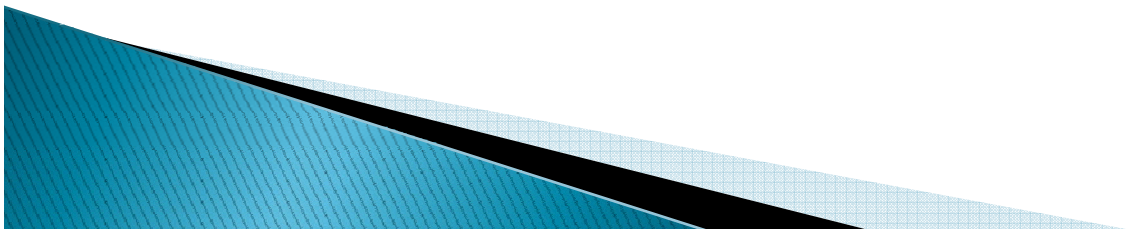
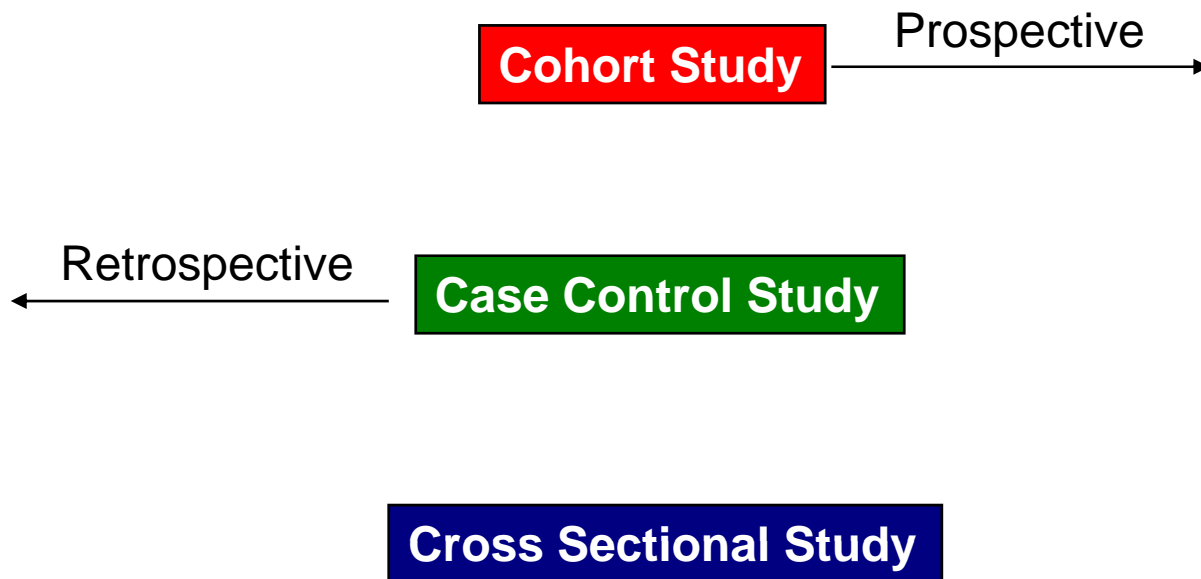
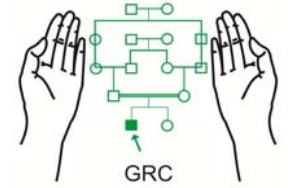
- For factors that **cannot** be controlled by investigators like age, sex, race etc.
- Essentially descriptive
- Most epidemiological surveys
- May be comparative
- May be prospective, retrospective or cross sectional

## ► Experimental

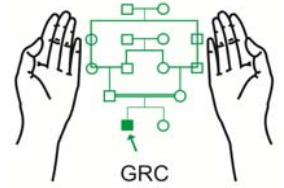
- For factors that **can** be controlled by investigators
- Always prospective
- Usually comparative
- Most clinical trials
- Inferences are stronger than observational studies



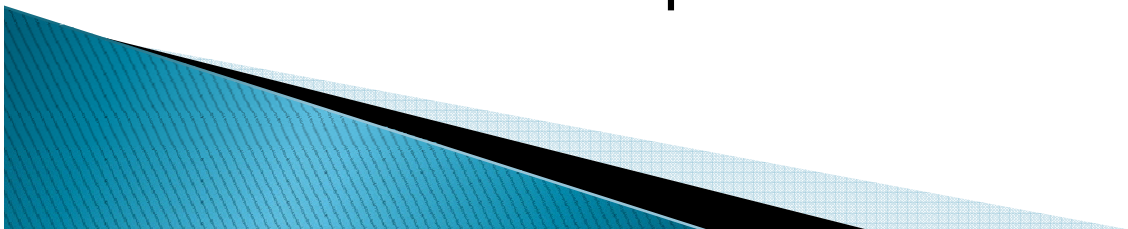
# Observational Studies



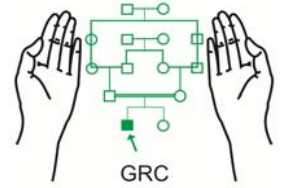
# Cohort Study



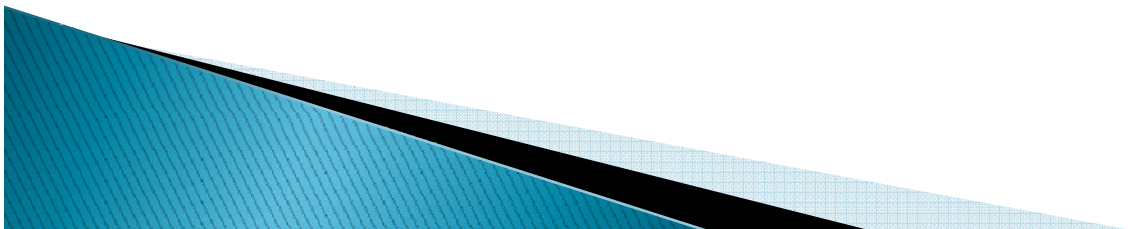
- ▶ A cohort (group) of subjects is identified
- ▶ Followed prospectively (longitudinal)
- ▶ Subsequent findings are recorded
- ▶ More than one cohorts may be studied and compared
- ▶ The best choice out of the observational studies
- ▶ Problems:
  - May be very long and expensive
  - Unsuitable for rare outcomes
  - Selection of subjects
  - Loss to follow-up



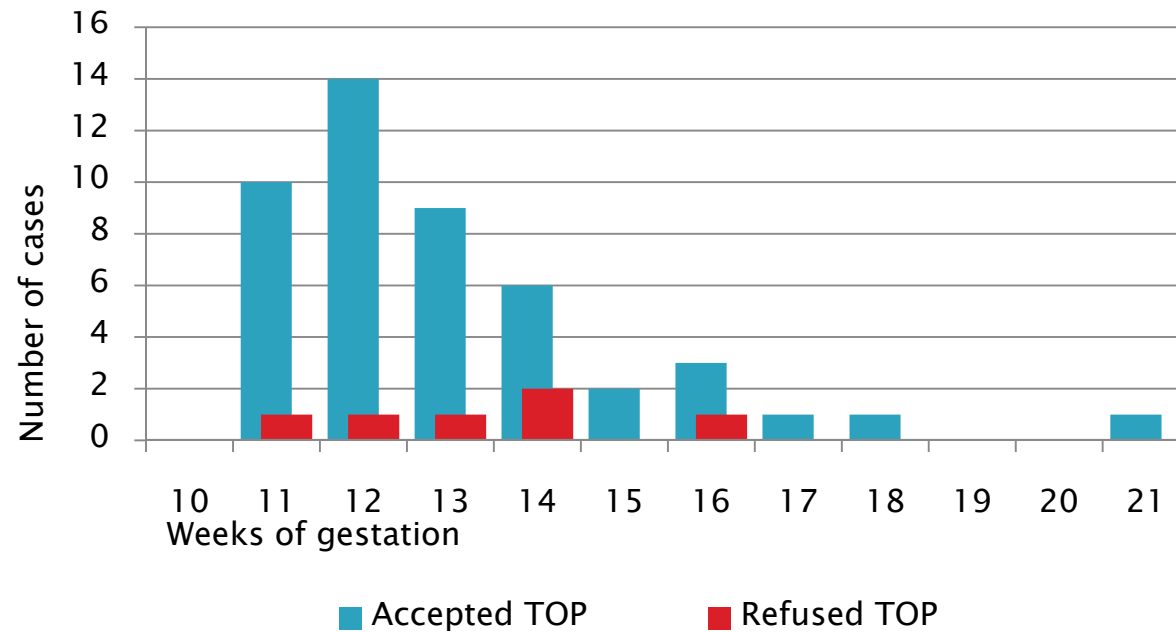
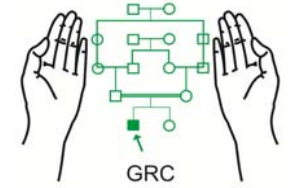
# Cohort Studies



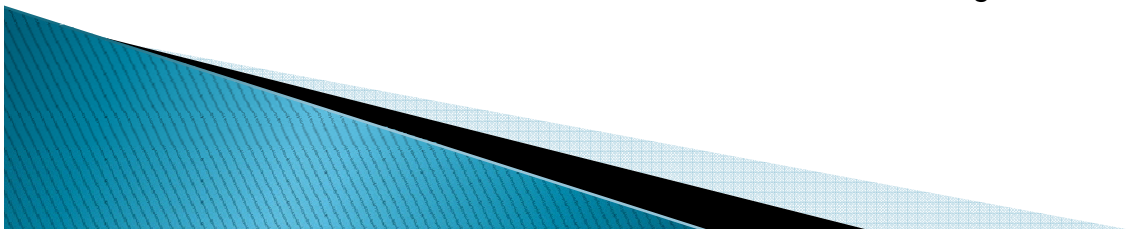
- ▶ Patients with Cirrhosis who develop Hepatocellular carcinoma
- ▶ Smokers and non smokers who develop Carcinoma lung
- ▶ Patients of Myelodysplastic syndrome who develop leukaemia



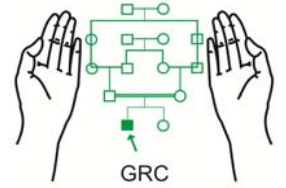
# Cohort Study



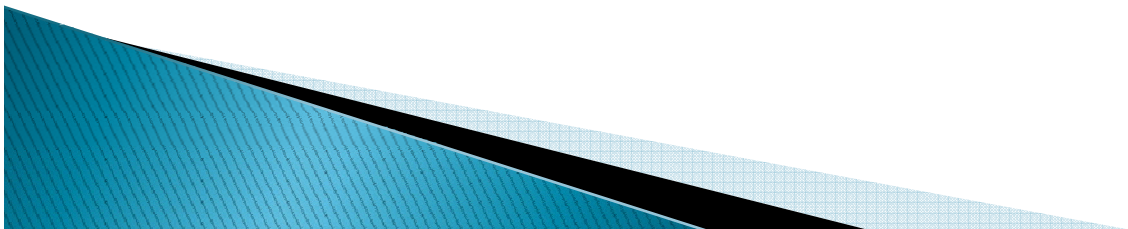
Prenatal diagnosis of  $\beta$ -thalassaemia in Pakistan: experience in a Muslim country.  
*Ahmed et al, Prenatal Diagnosis 2000; 20: 378-383.*



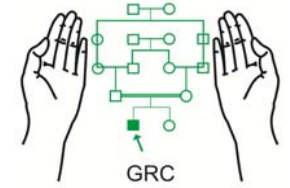
# Case Control Studies



- ▶ Always retrospective
- ▶ Simple and inexpensive
- ▶ Suitable for rare outcomes
- ▶ Problems:
  - Selection of controls
  - Selection of cases
  - Recall bias

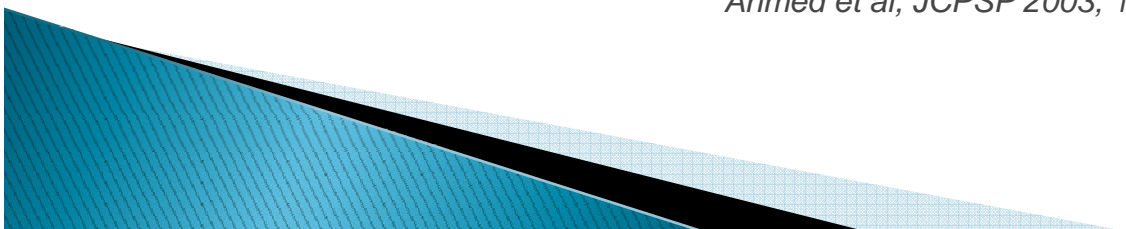


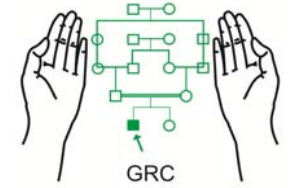
# Case Control Study



Haematological Parameters	Untransfused (n=171)		Transfused (n=109)		p value
	Mean	Range	Mean	Range	
Hb (g/dl)	6.3	1.9-9.0	6.2	2.3-11.2	0.20
MCV (fl)	70	57-83	74	58-98	0.014
MCH (pg)	21	15-29	24	16-31	0.015
Hb-F (%)	95	35-97	31	0.5-97	<0.001

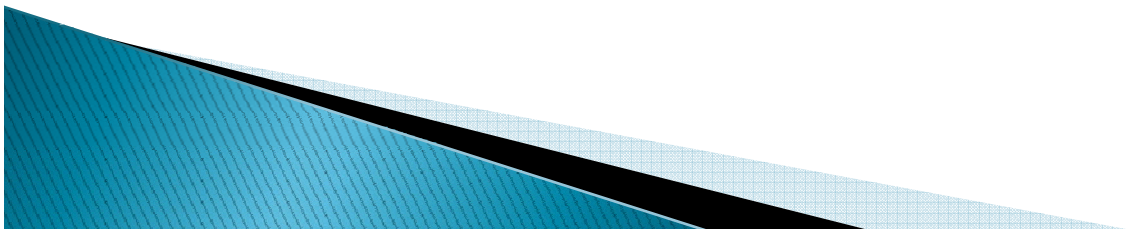
Diagnosis of  $\beta$ -thalassaemia major in previously transfused patients.  
*Ahmed et al, JCPSP 2003; 13: 19-20.*



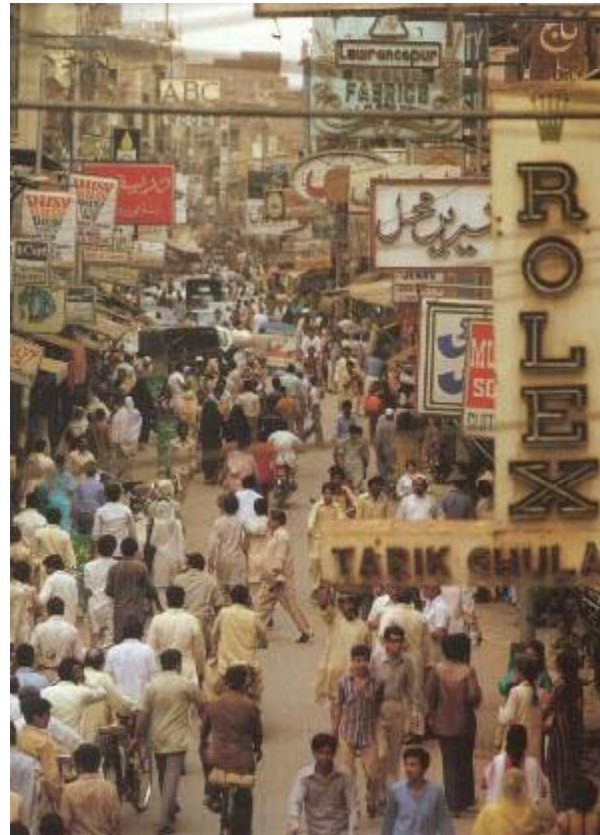
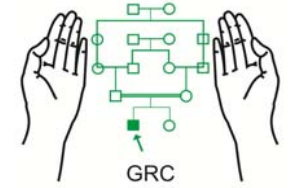


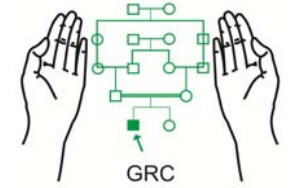
# Cross Sectional Studies

- ▶ Information is collected at only one point in time
- ▶ Most epidemiological surveys
- ▶ Easy and cheap
- ▶ May be used as an alternative to cohort or case-control studies
- ▶ Problems:
  - Sample selection

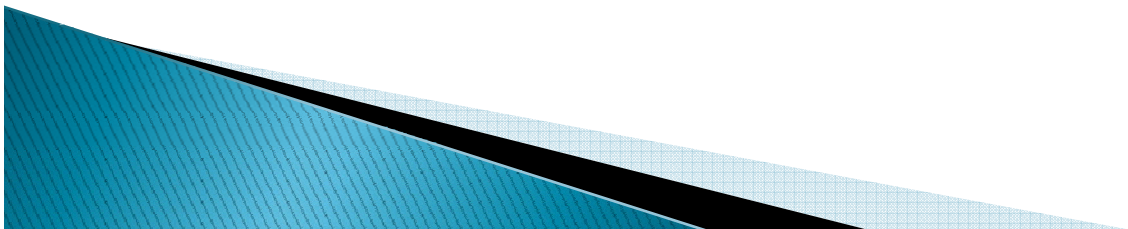


# Population

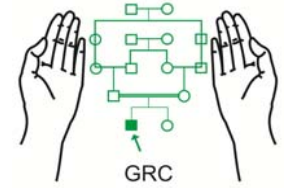




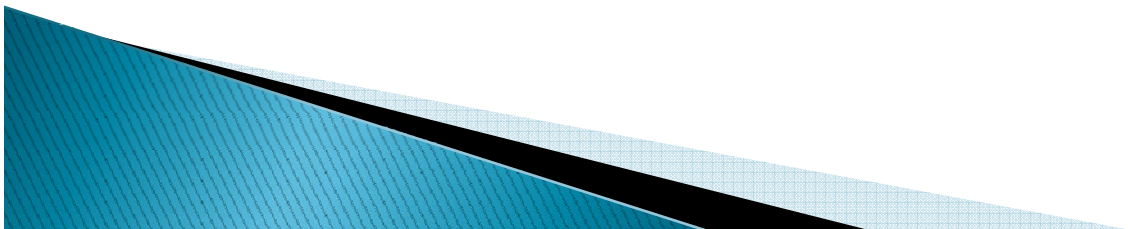
# Sampling Bias in Epidemiological Surveys



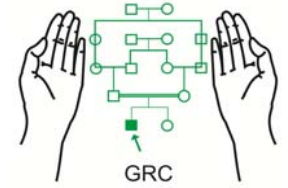
# People who travel from Rawalpindi to Lahore in one day



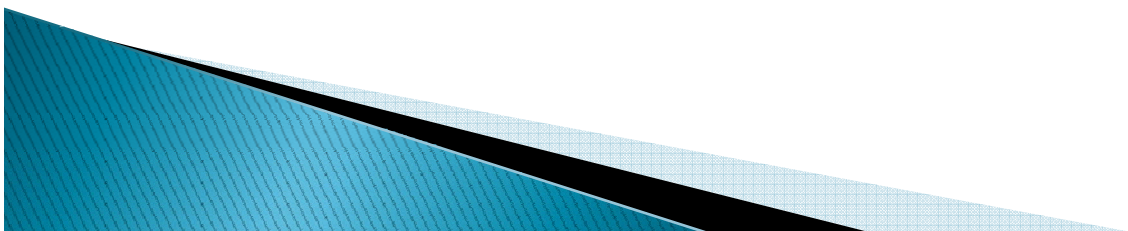
Place:	Yes:	No:
Train/Platform	90%	10%
Departure lounge	40%	60%
Parking	25%	75%
Bazar	1%	99%
Total:	39%	61%

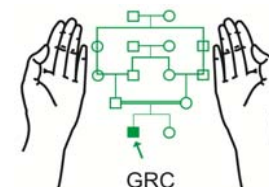


# Anaemic children in Rawalpindi



Place:	Anaemic:	Normal:
AFIP	55%	45%
MH	40%	60%
CMH	25%	75%
School	12%	88%
Total:	33%	67%



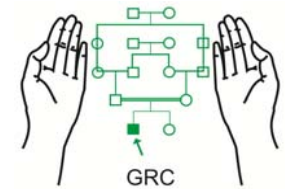


# PATTERN OF NEONATAL MORTALITY IN MILITARY HOSPITAL, RAWALPINDI

Department of Paediatrics, Military Hospital, Rawalpindi

## ABSTRACT

The study was undertaken to determine neonatal mortality rate (NMR) and pattern of diseases in our set up of Military Hospital (MH), Rawalpindi. Cohort study of all the newborns delivered in maternity ward of MH, over a period of 6 months was carried out. Follow up was done over a period of one month. NMR in our study population was 27 per thousand live births, 12% of all the babies were low birth weight and 5.9% were premature. Major causes of mortality were birth asphyxia, infections, respiratory distress and congenital infections. The results were comparable with other regional studies. The incidence of mortality, low birth weight and prematurity along with other complications is still high in our region of the world cost effective and simple measures should be adopted as a remedy.

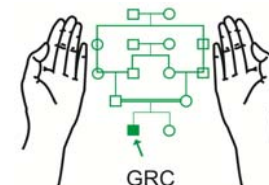


## GESTATIONAL TROPHOBLASTIC DISEASE: A STUDY

### Abstract

*A total of 27 cases of Gestational Trophoblastic Disease (GTD) including 24 of hydatidiform mole and 3 of choriocarcinoma were seen during a three year period. During this time, 5702 pregnant patients were admitted giving a rate per pregnancy of 1:211 or 4.74 per 1000.*

*Of the 27 cases, 9 (33.33%) mothers and 12 (44.44%) fathers were 40 years or over in age. Nineteen women (70.37%) were gravida 5 or over. No relation to specific dietary factors, age of menarche, contraception, blood groups or weight was elicited. No patient had pre-eclampsia, thyrotoxicosis or disseminated intravascular coagulation. Only one patient had excessive vomiting. None had metastatic disease. Twenty-two (81.48%) patients were anaemic, and 15 (55.55%) required at least two units of blood transfusion. Of patients with hydatidiform mole 16 (59.26%) had primary suction curettage, 7 D&C and 1 primary hysterectomy. Later, 1 patient with residual GTD required methotrexate, and another a hysterectomy. The three cases of choriocarcinoma were diagnosed on diagnostic D&C and were given MAC regimen. One later required a hysterectomy. Monitoring and follow-up of all except first five cases of GTD was done by serial serum beta HCG levels (JCPSP 1992;2(2):3-9)*

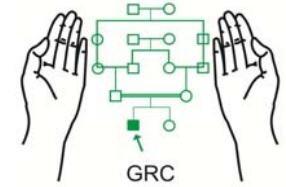


# INCIDENCE AND CLINICAL ASPECTS OF HEPATITIS B IN HOSPITAL KARACHI

## ABSTRACT

A total number of 3395 patients admitted in Karachi due to viral hepatitis during the past 3 years (Jan 1991-Dec 1993) were studied. The blood samples were analysed for various liver function tests, bilirubin, alkaline phosphatase, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). In selected cases, ultrasound, CT scan were performed to exclude other causes of jaundice. Hepatitis-B-surface antigen (HBsAg) was the primary investigation (Latex agglutination method) to identify positive cases. The main presenting symptoms were anorexia, malaise, fever, abdominal discomfort, and jaundice. Hepatomegaly (78%), splenomegaly (20%), pruritus (20%), and bradycardia (12%), were noted. Out of 3,395 cases, 472 (14%) were HBsAg positive. Nine patients died (0.26% mortality), main cause being fulminant hepatitis. Viral-B-hepatitis is a common infectious disease in Karachi which causes a lot of morbidity. Awareness is a must to minimise the incidence. Prevention is the only way to control this disease. Hepatitis-B-vaccination should be included in our immunization programme.

# Cross Sectional Study

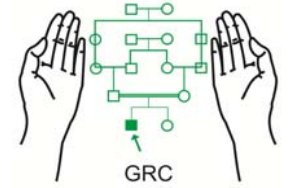


Mutation	Punjabi	Pathan	Sindhi	Baluchi	Mohajir	All
<b>Common mutations</b>						
IVSI-5 (G-C)	107 (27.2%)	27 (12.9%)	114 (43.9%)	131 (76.2%)	75 (41.4%)	454 (37.3%)
Fr 8-9 (+ G)	146 (37.2%)	103 (49.1%)	29 (11.2%)	14 (8.1%)	23 (12.7%)	315 (25.9%)
Del 619 bp	14 (3.6%)	4 (1.9%)	36 (13.9%)	2 (1.2%)	29 (16.0%)	85 (7.0%)
Fr 41-42 (-TTCT)	36 (9.2%)	18 (8.6%)	16 (6.2%)	1 (0.6%)	11 (6.1%)	82 (6.7%)
IVSI-1 (G-T)	19 (4.8%)	4 (1.9%)	33 (12.7%)	2 (1.2%)	7 (3.9%)	65 (5.4%)
<b>Uncommon mutations</b>						
Cd 15 (G-A)	14 (3.6%)	13 (6.2%)	5 (1.9%)	9 (5.2%)	8 (4.4%)	49 (4.0%)
Cd 30 (G-C)	15 (3.8%)	1 (0.5%)	19 (7.3%)	3 (1.7%)	4 (2.2%)	42 (3.5%)
Cd 5 (-CT)	11 (2.8%)	16 (7.6%)	0 (0.0%)	1 (0.6%)	2 (1.1%)	30 (2.5%)
Fr 16 (-C)	6 (1.5%)	8 (3.8%)	6 (2.3%)	6 (3.5%)	3 (1.7%)	29 (2.4%)
Cap + 1 (A-C)	9 (2.3%)	8 (3.8%)	0 (0.0%)	0 (0.0%)	3 (1.7%)	20 (1.6%)
Hb-E	3 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (5.5%)	13 (1.1%)
Cd 30 (G-A)	3 (0.8%)	2 (1.0%)	0 (0.0%)	2 (1.2%)	4 (2.2%)	11 (0.9%)
IVSII-1 (G-A)	6 (1.5%)	1 (0.5%)	0 (0.0%)	1 (0.6%)	2 (1.1%)	10 (0.8%)
<b>Rare mutations</b>						
-88 (C-T)	1 (0.3%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.3%)
IVSI-1 (G-A)	1 (0.3%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Fr 47-48 (+ ATCT)	2 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Fr 126-131 (-17 bp)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)
Cd 39 (C-T)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
IVSI minus 25	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
<b>Total</b>	<b>393 (100%)</b>	<b>210 (100%)</b>	<b>260 (100%)</b>	<b>172 (100%)</b>	<b>181 (100%)</b>	<b>1216 (100%)</b>

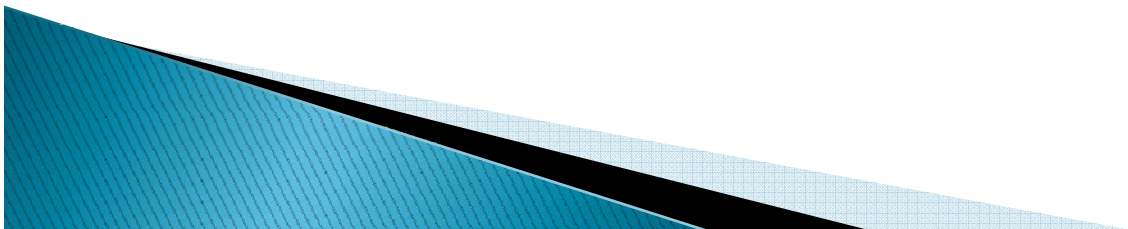
© 1996 Blackwell Science Ltd, *British Journal of Haematology* 94: 476-482

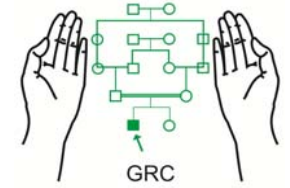
Molecular genetics of  $\beta$ -thalassaemia in Pakistan: a basis for prenatal diagnosis.  
Ahmed et al, *Br J Haematol* 1996; 94: 476-481.

# Sampling



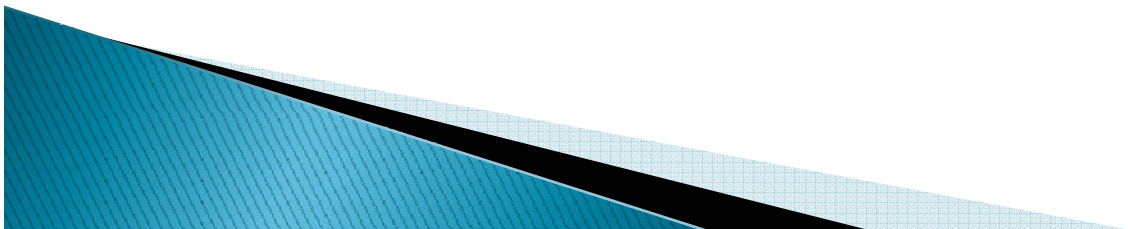
- ▶ The sample should be representative of the population
- ▶ Care in formation of “groups” with respect to known sources of variation
- ▶ Confounding Variables
- ▶ Adequate sample size

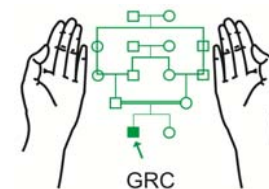




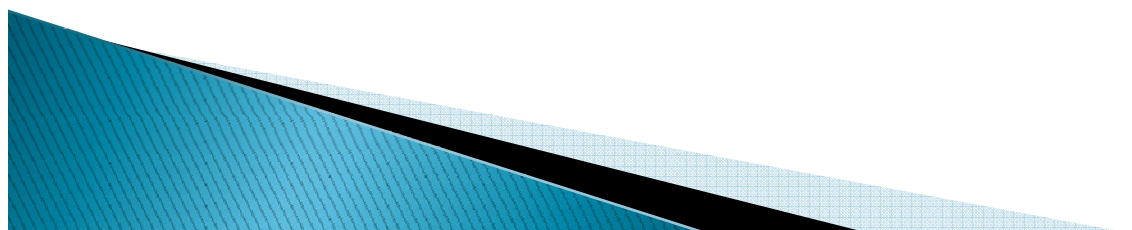
# Experimental Studies

» Randomized Controlled Study

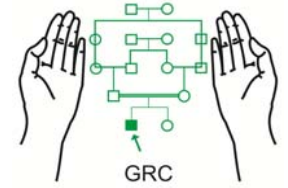




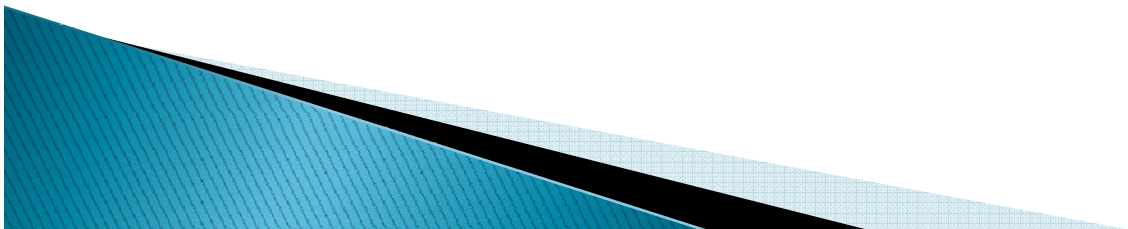
»» “Let’s try this new treatment on some patients and see what happens”



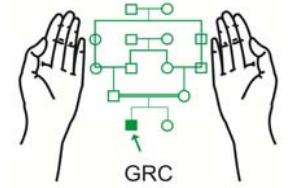
# Randomized Controlled Study



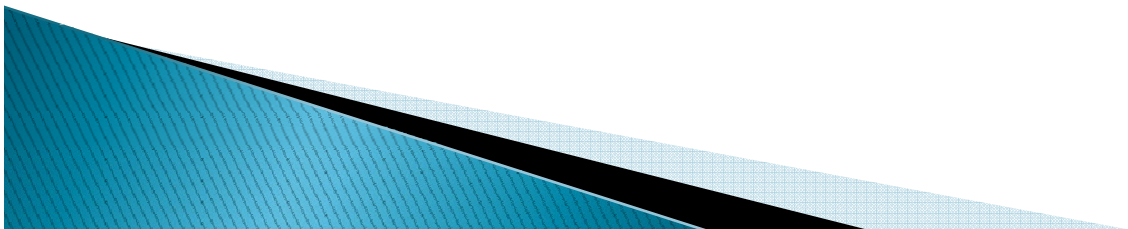
- ▶ Randomization
- ▶ Blinding
- ▶ Cross over
- ▶ Selection of subjects
- ▶ Selection of controls

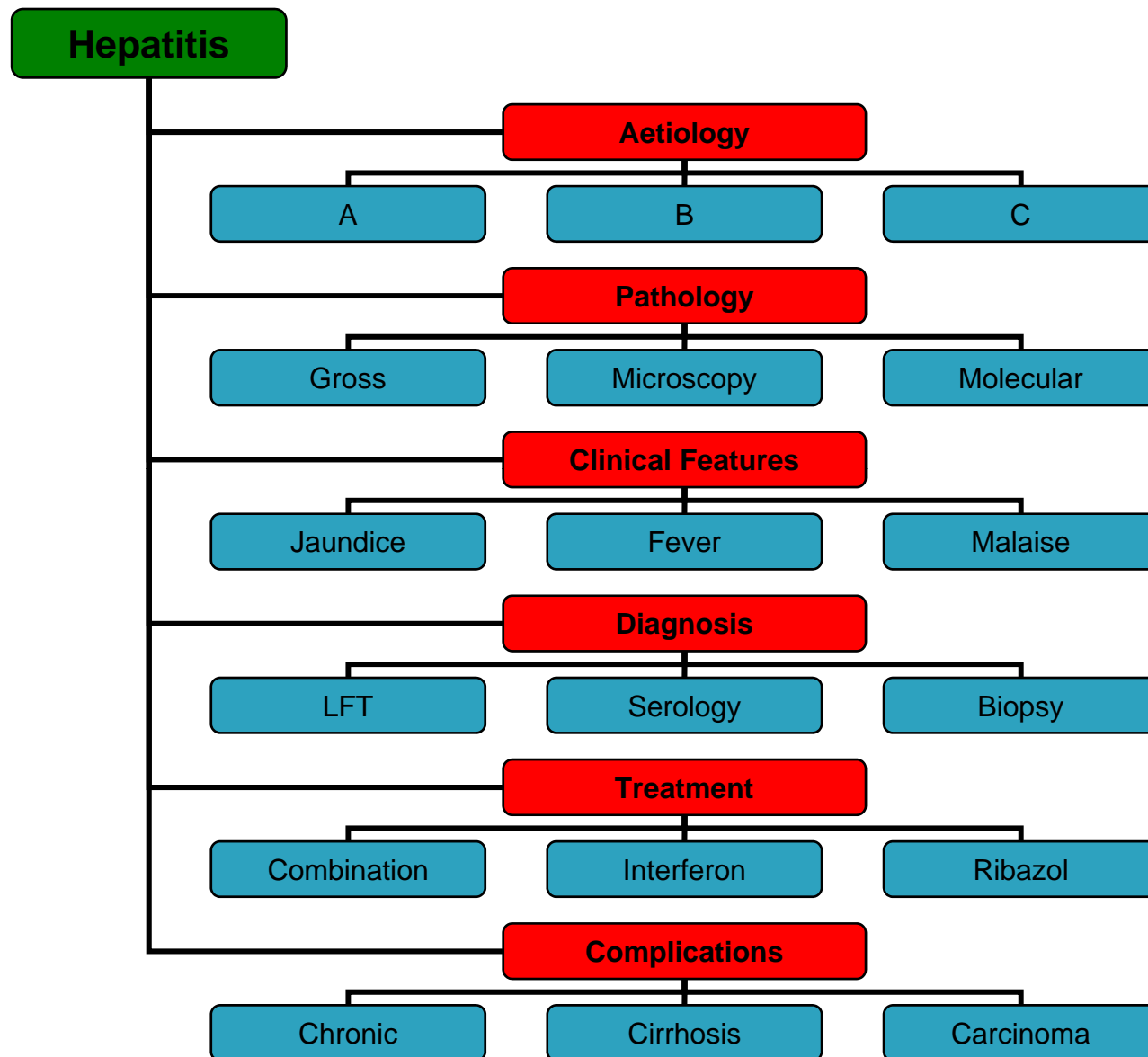
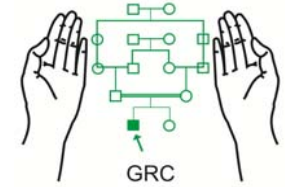


# Randomization



- ▶ Each patient has an equal chance of receiving the experimental conditions
- ▶ Simple randomization
  - Tossing a coin
  - Table of random numbers
  - Computer
- ▶ Block randomization
- ▶ Stratified randomization
- ▶ Cluster randomization





# Afterthought ?

The data from a good study can be analyzed in many ways, but no amount of clever analysis can compensate for problem with the design of a study.

(Altman, 1991)

