Summary
SUMMARY

Anxiety disorders are among the most prevalent psychiatric disorders in human population. These are characterized and accompanied by a number of physical signs, such as sweating, palpitation, Non-locomotive hyperactivity such as dryness of mouth, finger tapping or repetitive leg movements, stuttering, and halting speech, changes in pitch and other signs related to speech and voice pattern are often observed.

Anxiety may take several forms like; generalized Anxiety disorder (GAD), it may be experienced as an inexplicable feeling of impending doom, or as unfounded worried about numerous things etc.

Phobia or irrational fear of a situation, activity or object (i.e. Agoraphobia, social phobia, specific phobia)

Panic disorder where anxiety manifests as recurrent panic attacks, sudden rushes of fearfulness accompanied by a number of physical and cognitive signs and symptoms such as rapid heart beat, trembling, feeling of unreality and fear of dying.

OCD (Obsessive Compulsive disorder) where mind is flooded with persistent and uncontrollable thoughts and the individual is compelled to repeat certain acts again and again.

PTSD (Post Traumatic Stress disorders) showed acute anxiety and persistent trauma as the result of some accident or extreme tragedy.

For present study two of these (panic disorder and OCD) were selected. DSM IV criteria distinguish three types of panic attacks on the basis of the context in which the attacks occur:
Unexpected (uncued, spontaneous): The onset of such panic attack is not associated with a situational trigger (that is the attack occurs totally unpredictably "out of the blue").

- Situationally bound (cued and invariably occurring). The attack on exposure invariably results immediately on exposure to or in anticipation of situational trigger or cue (these attacks are totally predictable).

- Situationally predisposed (Cued but variably occurring): the attack is more likely to occur on exposure to the situational trigger but does not invariably occur and may not occur immediately after the exposure.

In the above definitions, the situational trigger may be any phobic stimulus i.e. any animal (specific phobia) or an activity for example, speaking before an audience (an individual with social phobia) or driving (in an individual having Agoraphoia). Situationally predisposed attacks are most common in patients with panic disorders with Agoraphobia.

In present study random survey was conducted on the diagnosed patients (probands) from the psychiatric centers of four medical colleges of North India. The probands were further diagnosed on the basis of questionnaire based on DSM-IV Criteria for Mental disorder having reliability 0.7% and their pedigrees were analysed for three to four generations to study the mode of inheritance, influence of genetic and/or environmental factors, penetrance and expressivity of the causative gene/genes. Random survey was also conducted on normal people (Surving as controls) selecting normal probands of almost equal age groups (Four age groups were considered, (group A, age range 0 to 15 years, group B 16-30 years. Group C 31 to 45 yrs and group D above 45 years. The pedigrees of these control probands were
also analyzed for 3 to 4 generations. A total of 123 pedigrees having the sufferer probands were analyzed for PD studies. Out of these, 80 pedigrees were also having the history of panic disorder these were considered as transmitting pedigree while 43 pedigrees were such where either only the proband or few relatives were showing the definite symptoms, such pedigrees were considered the precipitated forms.

The minimum age of onset was observed as 8 years and 13 years in a male and a female proband respectively the upper limit of age of onset was observed as 40 in one of the female and 42 in a male sufferer.

It was found that if the age of onset is early (before adolescence) the disorder shows severe symptoms with almost life long prevalence in spite of the treatment taken by the patient and the no. of sufferer relatives is high on the other hand if the disorder appears late the symptoms are few, less severe and number of sufferer relatives is small. Maximum sufferers were observed in group ‘C’ (between the age 30 to 45). In this population (unlike the previous reports from other populations) the frequency of definitely sufferer males and females was almost in the same range (11.1% in its and 10.7% in males). This shows that the pattern of inheritance is not sexlinked but is autosomal. The prevalence of genetic factor was calculated in I, II and III degree relatives of probands and control. Probands relatives were showing almost continuous an inheritance up to 2 to 3 generation this clearly suggested that the causative gene/genes have dominant nature and the disorder is familial. However observing various age of onsets and variable expressivity (in the form of definite, probable and possible sufferer individuals) with incomplete penetrance the disorder could not be categorized as monofactorial and Mendelian in nature though the ratios between sufferers and non-sufferers in II and III generations of transmitting pedigrees
are found in close proximity to classical 3:1 and 1:1 ratio and sibship studies are also proving it (presence of considerable no. of sib trios and sibtetras) yet the variable expressivity normal distribution and incomplete penetrance, all reflect that there is a mixed genetic model working for the disorder. The major loci (i.e. 9q, 13q and 22q and few minor, loci (8q, 12q, 7p, 14p, etc.). seem to be responsible for the disorders as observed in these segregational studies.

The disorder was also showing high comorbidity with Agoraphobia, which is considered the major complication in the suffers of panic disorders. The decision made in DSM-III-R to include Agoraphobia as a subtype of panic disorder was retained in DSM-IV, it was found among the definitely and probably sufferers that sufferers of PD with Agoraphobia show more severe condition as compare to PD. Patients without Agoraphobia. Besides this, comorbidity among the P.D. Patients was also noted for GAD, specific phobia and PTSD, reflecting the conditions of linkage i.e. the genes responsible for these psychoneurotic disorders are also suspected to linked with P.D. genes and it is also confirmed from the studies of Gelernter et al.2001 and 2003 that gene locus on 3q for Agoraphobia also has the linked gene for PD and specific phobia whereas gene loci 14p, 8q, 3q are main loci for specific phobia linked with panic disorder gene or genes (small stretches on chromosome 1q, 9q and 10q.). Double comorbidity was also observed in one male and 8 female for agoraphobia and GAD. These suffer very severely for panic attacks and were found almost confined to their homes.

Besides transmitted cases there were also observed precipitated cases in 43 pedigrees the precipitation of PD either only in proband or in very few of their relatives with some of these above mentioned psychoneurotic disorders (Agoraphobia,
specific phobia GAD and PTSD. However in 32 pedigrees there were no comorbidities. These pedigrees were showing such sufferers who were not showing any history of transitions. Therefore, these were considered as either the spontaneously originated cases due to spontaneous gene mutation or they were the phenocopies (the reason of attack was any other than genetic like Mitral valve prolapse, (MVP) severe heart and blood pressure problems, kidney and prostate disfunctioning etc.).

Survey was conducted on 107 twin pairs, results in 20 and 26 twin pairs suffering from panic disorders and obsessive compulsive disorder respectively. The twins were classified in MZ (Monozygotic and Dizygotic). The MZ & DZ twin pairs were further classified into reared together and reared apart. The higher value of the concordance for the MZ twins (82.12%) as compared to the concordance of the DZ twins 51.20% proves that genes play major role in the cause of the disorder. Further proof of its genetic nature is obtained by analyzing the value of MZ twins reared apart which shows quite high concordance proving that the role of environmental factors is secondary as compared to the influence of genes is causing the disorder, the inheritance of relatives (first, second and third degree) and existence of sib ship proves the dominant, highly penetrant and expressible nature of gene. The twin analysis shows that value of heritability of panic disorder is 61.84%.

Obsessive compulsive disorder is another Anxiety disorder in which mind is flooded with persistent and uncontrollable thoughts or the individual is compelled to repeat certain acts again and again causing significant distress and interference with every day functioning.
Obsessions are intrusive and recurring thoughts impulses and images that come unbidden to the mind and appears irrational controllable to the individuals experiencing them.

A compulsion is a repetitive behavior that the person feels driven to perform in order to reduce distress or prevent some calamity from occurring.

Survey was conducted randomly on 152 families, comprised of 2497 individuals out of 152 families, 36 were those in which disease is precipitated due to various reasons. 50 control pedigrees were also analyzed for the presence of OCD, where the age range of control was same as sufferer probands. A total 428 individuals were interviewed and the only one definite sufferer was seen in one pedigree.

The pedigrees were analyzed for mainly three generation with the exception of the pedigrees in which four generations were studied to study the interaction penetrance and expressivity experienced.

The numbers of female proband was found to be far more as compared to male probands in both transmitted as well as in the precipitated cases. The mode of inheritance was found to be continuous in >60% of the pedigrees in ratio of 3:1 and 1:1. The disorders affect both male and female children and occur continuously generations after generation. Thus showing its dominant nature the data shows that the disorder is more prevalent in females as compared to males. The detailed study of due disorder suggested that both male and female transmit the disorder to both the type of children. i.e. the disorder is neither showing crisscross nor holandric inheritance. Thus, proving it as autosomal and discarding the sex linkage, there are also certain pedigrees in which one or two persons were found to be affected by OCD.
such precipitated cases were the results of some spontaneous mutation or are the phenocopies.

The present study also shows a very remarkable characteristic of OCD i.e. the occurrence of comorbidity with other psychoneurotic disorders Tourettes disorder, depression, phobia and GAD, the maximum comorbidity of OCD found with Tourettes disorder.

Survey results were also conducted on 107 twin pairs the 26 twins pairs which were. Of found to be suffering from OCD were further classified into MZ (Monozygotic) and DZ (dizygotic). There were about 11 MZ twin and 15 DZ twin pairs. The MZ & DZ twin pairs were further classified into reared together and reared apart.

The higher value of concordance for MZ twins 81.70% as compared to the concordance of DZ 48.81% proves that genes play a major role in the cause of the disorder. The concordance value is also calculated for MZ twins reared together and reared apart and found that concordance value for MZ twins reared apart shows elevation, proving more roles of genic factors and the environment plays a secondary role in the cause and occurrence of the disorder.

Twin analysis was also used in the calculation of heritability, and the value obtained is in the ranges i.e., 65.78% for OCD.