Summary
INTRODUCTION

Drug abuse refers to the use, usually by self-administration, of any drug in a manner that deviates from the approved medical or social patterns within a given culture. It may originate with the physicians, the patient seeking medical treatment, or with adolescent drug experimenter. Drug abuse is, therefore, not a new phenomenon. Opium, *Cannabis Sativa* (Bhang, Ganja, Charas), Alcohol (Somras) etc. have been used as abusive drugs from the historic time. However, with the recent development in science, many more synthetic drugs have been formulated, which are being used for abusive purpose.

Though estimating the hazards caused by these abusive drugs, most of these drugs have been banned in our country under the Narcotic Drugs and Psychotropic Substances (NDPS) Act (1985), yet still there are some recently synthesized abusive drugs which are not included in the list of Schedule II of NDPS Act. Amidst these synthesized abusive drugs, pentazocine is a recently developed non-narcotic drug, which is usually chosen by pleasure seeking drug addicts due to its easy availability from the market.

Pentazocine is a synthetic non-narcotic analgesic drug, which is about one-third to one-sixth analgesic potential as
morphine. It was first synthesized and studied by Archer et al. in 1962 and prescribed as an analgesic drug around 1970. It is an important analog of benzomorphan derivatives, which has a simplification of morphine skeleton as shown below.

![Morphine and Pentazocine structures](Image)

Pentazocine is a well-known agonist and antagonist mixed opioid drug, which interacts with three major opioid receptors of Central Nervous System (CNS). It interacts with σ (sigma) and K (Kappa) as weak to moderate agonist. Pentazocine resembles with morphine in agonistic pharmacological effects and has psychotomimetic effects such as uncontrollable thoughts, anxiety, nightmares, hallucination and euphoria. Pentazocine interacts with μ (mu) as a weak antagonist, so it may be used in the treatment of narcotic physical dependant patient.

It became popular in addict subculture after 1980. Until recently, pentazocine has not been included in the list of Schedule II of Narcotic Drugs and Psychotropic Substances
(NDPS) Act of India, hence it is widely abused due to its easy availability in the open market.

It has been reported by many workers, that pentazocine causes tolerance and physical dependence. Some pharmacological and behavioral changes have also been observed. The drug becomes toxic when taken in overdose for prolongation. Thus, some adverse effects on biochemical constituents of some body tissues may be observed due to chronic pentazocine administration.

THE PRESENT WORK

Hence, realizing the significance of pentazocine as an abusive drug amongst drug addicts, a research work envisaging the pharmacological and biochemical studies of chronic pentazocine administration has been undertaken in the laboratory.

MATERIALS AND METHOD

Fortwin, in the form of pentazocine injection and healthy adult albino rats of both sex as experimental animals have been selected for the present study. The drug was given to different groups of albino rats intramuscularly with daily dose of 0.05mg 100 gm⁻¹ (½ED₅₀) for the period of 30, 60, 90, 120, 150 and 180 days respectively.
I. Pharmacological Study

The following agonistic pharmacological properties due to chronic exposure of pentazocine have been studied.

A. Effect on CNS: To study the influence of pentazocine on CNS, the following parameters have been considered.

1. Analgesic Study: The analgesic response of albino rats was measured by tail-flick method using an Analgesiometer (Techno, Lucknow, India).

2. General Gross Behaviour: It included the following studies.

(a) Sedation: The sedative effect of pentazocine was observed in the form of changes of overt behaviour i.e. spontaneous motor activity and aggressive behaviour.

i). Spontaneous Motor Activity (SMA): The spontaneous motor activity (horizontal activity) has been measured by using Actophotometer (Techno). The changes in the motor activity have been observed and recorded.

ii). Aggressive Behaviour: The study of aggressive behaviour of animals has been performed by using Aggressiveness Test Chamber (Techno). The time taken by the animal to show aggressive behaviour has been recorded.
(b) **Drowsiness:** The drowsiness effect of pentazocine was observed by normal examination of the time period of closed eye of the experimental animals.

(c) **Compulsive Behaviour:** In this study stereotype behaviours i.e. repetitive standing, continuous sniffing and licking the wall of container was observed and time period of the particular compulsive behaviour was measured.

(d) **Learning Behaviour:** It was observed by using a Habb William’s Maze or Y-Maze (Techno). The time taken by the drug administered animals to run through the maze have been recorded and compared with control sample.

**B. Study Pertaining to Physical Dependence:** In this study the development of physical dependence induced by pentazocine was determined by measuring the body weight of the pentazocine withdrawal animals vs. control animals.

**C. Study Pertaining to Withdrawal Symptoms:** It included the study of symptoms of pentazocine withdrawal animals viz. lachrymation, rhinorrhoea, fever and restlessness etc. The symptoms viz. lachrymation, rhinorrhoea and restlessness were observed by normal observation, whereas febrile condition was measured by the body temperature using a thermometer at the rectum of the animal.
II Biochemical Study

Under this scheme the adverse effects of chronic pentazocine administration on biochemical contents of some body tissues have been studied in the form of \textit{in-vivo} and \textit{in-vitro} studies.

A. \textbf{In-Vivo Study:} It has been performed in the form of estimation of various constituents of blood with the respective suitable method. The blood sample was collected from different groups of rats after completion of respective period of drug administration. Later on the estimation of the following constituents in blood was done by using suitable methods-


2. \textbf{Serum Globulin:} Biuret Reagent Method.


5. \textbf{Serum Bilirubin:} Dazo Reagent Method.

6. \textbf{Serum Glutamate Oxaloacetate Transaminase (SGOT):} Reitman-Frankel Method.

7. \textbf{Serum Glutamate Pyruvate Transaminase (SGPT):} Reitman-Frankel Method.

8. \textbf{Acid Phosphatase:} Gutman and Gutman Method.

**B. In-Vitro Study**: The changes in protein, glycogen, RNA and cholesterol contents in brain, spinal card, liver and kidney have been performed under this study. The tissues were isolated from different groups of animals and processed for the estimation of above biochemical constituents by using suitable methods.

(i) **Protein**: Biruet Reagent Method.

(ii) **Glycogen**: Anthrone Reagent Method.

(iii) **RNA**: Orcinol Reagent Method.

(iv) **Cholesterol**: Lieberman-Burchard Method.

**III. Drug Accumulation Study**

If the rate of drug intake is constantly regular and the rate of output is exponential, then some content of the drug will deposit in the system until a steady state is reached.

Hence, the accumulation phenomenon was also studied in the present work. As such pentazocine has been found accumulated in the vital organs such as liver, brain and kidney in the present study in a considerable amount, which was calculated by TLC using the spot area vs concentration calibration graph method.
RESULTS, DISCUSSION AND CONCLUSIONS

1. Pharmacological Study

The following results are obtained from the pharmacological observations:

A. Effect on CNS: The results of pentazocine administration effect on the CNS are given as follows.

1. Analgesic Study: It has been found that the repeated administration of pentazocine has a significant analgesic effect after the period of 30 days. The drug administered rats showed approximately three fold analgesic property than control rats, even during the initial period of 30 days, which showed a slight decrease during the later duration. It is probably due to the interaction of drug with CNS receptors. Moreover, a slight decrease in analgesia during the later period may probably be from the development of cellular adaptation of the body system.

2. Study of General Gross Behaviour: The following results have been obtained.

(a) Sedation: The results of pentazocine induced sedative effect are given as follows.

i). Spontaneous Motor Activity (SMA): The results revealed that pentazocine reduces the locomotion activity of albino rat through depression of CNS. It has been highlighted by a remarkable decrease in mean score of drug treated animals
during the time span of 30 to 180 days viz. 199.7 to 215.8 as compared to 270.5 mean score of control animals.

ii). **Aggressive Behaviour:** The results elucidated that the drug depresses the aggressive behaviour of albino rats considerably due to its prolonged intake.

The study of overt behaviours i.e. SAM and aggressive behaviour clearly indicates that pentazocine produces sedation. Probably it is due to the drug interaction with K (Kappa) opioid receptor of CNS (Goodman and Gilman, 1985; Tripathi, 1988).

(b) **Drowsiness:** Pentazocine also produces drowsiness in some cases after acting on K (Kappa) opioid receptor of albino rat, which is obvious from the present observations.

(c) **Compulsive Behaviour:** These stereotype behaviours are due to the interaction of drug with neurotransmitter receptor, dopamine. In the present study, very low compulsive behaviour has been observed with drug treated sample and control group. Hence, it is concluded that pentazocine does not influences the concerning receptor appreciably.

(d) **Learning Behaviour:** Pentazocine administered albino rats showed a modulated learning behaviour, because they took more time to run through the William's maze in comparison to control animals.
B. Study Pertaining to Physical Dependence: The pentazocine withdrawal groups of albino rats did not show significant loss of body weight during the drug termination period. Thus it is inferred that pentazocine produces negligible physical dependence amongst the drug abusers.

C. Study Pertaining to Withdrawal Symptoms: The results revealed the fact that the withdrawal symptoms viz. lachrymation, rhinorrhoae, fever and restlessness are not found significantly amongst the pentazocine withdrawal albino rats. Thus, it is concluded that pentazocine produces negligible withdrawal effects on the body organs.

The detail results of pharmacological studies of pentazocine abuse are discussed extensively in the thesis.

II. Biochemical Study

A. In-Vivo Study: The in-vivo study of different constituents of blood of the pentazocine treated animals vs control enunciated the following conclusions.

1. Blood Glucose: The continuous administration of pentazocine induced hyperglycemia after 30 days of drug administration (e.g. 72.33 ± 2.36 mg dl⁻¹ whereas the control had 64.97 ± 2.36 mg dl⁻¹). The glucose level remained almost steady during the later period (e.g. after 180 days the glucose level was 72.85 ± 2.33 mg dl⁻¹). It may probably be due to the
effect of drug at some stage of glucose metabolism, glucose conversion or transportation, during this period.

2. **Serum Globulin and Albumin:** The drug administered groups of albino rats have shown significant depletion of protein after 30 days of drug treatment. For example, globulin in control was $2.91 \pm 0.15 \text{ mg dl}^{-1}$ whereas in drug administered animals it was $2.22 \pm 0.11 \text{ mg dl}^{-1}$. So also albumin in control rats was $3.88 \pm 0.15 \text{mg dl}^{-1}$ but in pentazocine treated rats it was $3.19 \pm 0.11 \text{ mg dl}^{-1}$. The globulin depletion becomes more pronounced during the later period (e.g. $1.95 \pm 0.11 \text{ mg dl}^{-1}$ after 180 days). But serum albumin level remained steady for the remaining period. These two serum proteins i.e. globulin and albumin are the important binder of xenobiotics. Probably pentazocine influences the biosynthesis of these proteins, which results in their significant depletion.

3. **Serum Cholesterol:** The slight hypercholesterolaemia in the pentazocine administered albino rats has been observed after 30 days of exposure period (e.g. Control had $137.09 \pm 2.15 \text{ mg dl}^{-1}$ whereas drug treated had $141.34 \pm 2.21 \text{ mg dl}^{-1}$) which was aggravated during the later period (e.g. $143.80 \pm 2.18 \text{ mg dl}^{-1}$ after 180 days). It may be due to the activation of acetyl coenzyme A or involvement of certain amino acids in cholesterologenesis (Jain, 1986, 1987, 1990 and Shrivastava et al., 1986).
4. **Serum Bilirubin:** A slight hyperbilirubinaemia was found amongst the pentazocine administered groups of albino rats after 90 days of drug treatment (e.g. Control had $0.72 \pm 0.05$ mg dl$^{-1}$ whereas drug administered animals showed $0.79 \pm 0.03$ mg dl$^{-1}$), which remained almost same during the later period of study. It is due to the interference in the bilirubin metabolism at some point between its production in the reticuloendothelial system and its excretion into the bile.

5. **SGOT and SGPT:** The level of both enzymes had increased significantly after 60 days of drug exposure, which remained almost unchanged in the remaining period. These two enzymes are the important biological indicators of hepatic injury.

6. **Serum Acid and Alkaline Phosphatase:** After the study, the level of the acid phosphatase enzyme has not been modulated significantly. However, the level of alkaline phosphatase was changed significantly after 150 days of pentazocine administration.

**B. In-Vitro Study:** The *in-vitro* study of different biochemical constituents revealed the following information.

(i) **Protein:** The experimental tissues i.e. brain, spinal cord, liver and kidney showed significant depletion of protein contents after 30 days of exposure which became more prominent during the later period (e.g. Liver protein content
after 30, 60, 90, 120, 150 and 180 days of exposure to pentazocine was 96.43 ± 1.49, 95.10 ± 1.50, 94.43 ± 1.96, 93.72 ± 1.72, 92.46 ± 1.83 and 91.75 ± 1.74 mg gm⁻¹ respectively against 104.39 ± 1.62 mg gm⁻¹ of control. The depletion of protein content was found in the following order liver > brain > spinal cord > kidney.

(ii) Glycogen: The drug treated animals showed significant depletion of glycogen contents after 30 days in liver and 60 days in all tissues. The depletion became pronounced during the later period of study but in spinal cord the depletion remained firm even after 180 days of exposure. The glycogen depletion in the different organs was found in descending order as liver > brain > kidney > spinal cord. It is asserted that it influences at some step of glycogenolysis or gluconeogenesis.

(iii) Ribo Nucleic Acid (RNA): It has been found that there is a significant decrease of RNA content in the brain, spinal cord, liver and kidney after 60 days of pentazocine administration. The depletion remained almost constant during the later period. The modulation of RNA contents may be due to the interference of drug at some stage of RNA synthesis. The remarkable modulation of RNA content in the tissues was found in succession as liver > brain > spinal cord > kidney.

(iv) Cholesterol: A slight hypercholesterolaemia was observed in the pentazocine treated tissues viz. brain, spinal
cord, liver and kidney after 90 days of drug administration which was aggravated in liver and kidney during the last phase of drug administration. But in brain and spinal cord the hypercholesterolaemia remained steady during the remaining period. After the completion of 180 days, the quantity of cholesterol increased in the order of liver > kidney > brain > spinal cord.

All these results are discussed in details in the thesis.

III Drug Accumulation Study

The results revealed that the liver had a strong deposition of drug whereas the brain and kidney had comparatively less accumulation of pentazocine after the completion of 180 days of drug administration period.

The detailed results are compiled in the thesis.

Thus, from the present work it is concluded that chronic pentazocine administration for a considerable period not only produces behavioural changes but also culminates into some significant haematological and biochemical changes in the vital organs.

The in-vivo and in-vitro studies of some blood constituents and protein, glycogen, RNA and cholesterol contents of vital organs such as brain, spinal cord, liver and kidney have elucidated these facts vividly.
In nutshell these haematological and biochemical fluctuations may influence the biopharmacokinetics of the body system, which may be injurious to the individual health.