DISCUSSION
If one looks back at the history, it seems that the desire to increase physical and mental performance is an inherent desire of human beings. It existed even when the life was not competitive. The popularity of caffein containing drink is testimony to man's quest for increasing his performance.

Caffein is found in large number of plants e.g. *Coffea arabica*, *Thea sinensis*, *Theobroma cacao*, *Paullinia sorbilis* and Kola nuts. These plants containing caffein are widely distributed. Wherever, these plants are indigenous, the natives have discovered their use as a beverage without the aid of any laboratory. As chance would have it clinical as well as laboratory research has documented the effect of caffein in enhancing the human performance (Weis and Laties, 1962). Caffein containing beverages like coffee, tea, cocoa and cola drinks are almost used universally. 'Mate' which contains caffein is the national drink of South American countries. Beverages of *Paullinia Sorbilis* is used by the natives of Amazon Basin. Natives of Sudan chew Kola nuts as well as drink its extract.

The popular legends describing the discovery of caffein drinks indicate that they are being used since the dawn of civilization. There is a legend regarding the discovery of tea by Bodhirama in the 6th century A.D.
Bodhirama was son of a King of India. He became apostle of Buddhism and travelled to China to spread the gospel of Budha. In China he lived in the open, tamed his passion, modified his flesh and ate only leaves. He did TAPASYA by deciding to stay awake for nine years to contemplate the virtues of Lord Budha. After three years of TAPASYA, he fell asleep. On awakening in a bid to do PRASCHIT, he pulled out his eye lids. The plant grew from the site where he threw his eye lids. This happened to be the plant of tea. He ate the leaves of the tea plant which gave him so much energy that he could complete his TAPASYA with renewed vigour. There is also a story regarding the discovery of coffee with a similar motive for the use of coffee as for the tea. Shepherds reported to an Arabian prior that the goats which had eaten the berries of coffee plant did not rest but were playing, were lively and were leaping about briskly all through the night. The prior instructed the shepherds to collect the berries. He drank the beverage of berries in a bid to do long prayers at night.

These legends regarding the discovery of caffein drinks do reveal even the quest of those men who had renounced the world to achieve solace to enhance their
performance. They were neither being in the competitive world nor aiming at any competition.

The trees belonging to Erythoxylon species contain cocaine and are indigenous to Peru and Bolivia. Natives of Peru and Bolivia have been using the Erythoxylon leaves since centuries to increase the endurance. Nearly 9 million kilograms of these leaves are consumed annually by about 2 million inhabitants of the high land of Peru (Ritchie and Cohan, 1975). Wilson, Schild and Modell (1975) have recorded: 'For several centuries the chewing of coca leaves has been a traditional custom in certain Andean regions of South America and it is estimated that about six million inhabitants of these areas follow this practice without any harmful effects'. But these remarks do not apply to pure alkaloid cocaine which is a drug of addiction. The same authors (Wilson et al., 1975) record: 'About 1880 the alkaloid cocaine was introduced as a cure for morphine dependence in America and Europe but it was soon discovered that the cure was worse than the disease. Cocaine abuse became a serious problem.'

Thus, the consumption of plants containing alkaloids capable of increasing the mental and physical performance and endurance can be traced to even the prehistoric era.
Thus, it is quite natural that athletes who are most of the time facing the extreme competitive situation where personal financial gains as well as personal and national prestige is at stake, would not miss the chance of using the drugs capable of enhancing endurance. So, the most publicised, the most active (so far atleast) and most widely studied (under controlled conditions on physical performance of military personnel as well as the athletes) drug amphetamine was used and abused by the sportsmen to improve their performance to the extent that some fatal outcomes among the sportsmen during the competition were attributed to the consumption of amphetamines (Laurence and Bennet, 1980). Ultimately, the use of drugs to enhance physical or mental performance (doping) was banned by international organisations responsible for arranging the international sports meets. Sportsmen resorted to the substitutes for amphetamines and the list of drugs banned for the purpose of 'doping' as declared by I.A.A.F. and other international organisations grew in number. Unfortunately with the exception of amphetamines and caffeine, no studies have been undertaken on the action of these 'banned drugs' used by or alleged to be used by the sportsmen for increasing the mental or physical performance. One is tempted to think that use of these drugs may be based merely on guess
work. Even no detailed studies have been done on the mechanism of action of the most widely studied drug amphetamine as far as the physical performance is concerned. The possibility can not be ignored that the drugs banned for doping in sports may not be having beneficial effect on the ultimate performance or having even negative effects on the physical performance. But a sportsman may have to deny himself the benefit of these drugs even he may be in the need of these drugs on valid medical grounds. The present study was prompted by an event which took place in 1972 Olympics. Ephedrine is commonly used in the treatment of bronchial asthma. An asthmatic player earned a gold medal but he was deprived of the earned gold medal as well as participation in the competition. (Williams and Thompson, 1973). Thus, it was considered worth while to re-evaluate the drugs which are banned to be used before or during the sports competition. Because, ephedrine has come to the lime light it was selected as a first drug to be studied. Ephedrine, containing fauna remains to be oldest plants used as a drug by the mankind. It is clear from the pages of history that the fauna containing the drugs (caffein and cocaine) capable of increasing the physical performance never escaped the common sence of ancient men and they are still being used to-day. But
we could not come across any reference or legend that the ephedrine containing plants have ever been used for enhancing the physical or mental performance. No doubt that like amphetamines, ephedrine is a sympathomimetic amine and like the former is having a C.N.S. stimulant action (the action of ephedrine on C.N.S. is much less marked as compared to the amphetamines). But guess work cannot solve the problems of drug action. There is lot of truth in the old satire that: 'we are pouring drugs about which we know little into the body about which we know nothing.' As far as effects of drugs are concerned, views of Dr. G.B. West Carry a lot of weight. According to him, 'as far as biological actions are concerned, the shortest distance between two points is not a straight line but a very sinuous curve' (West, G.B. Cit Singh, G.S., 1963). The only way to prove or disprove any claim about the drug action is to conduct well controlled and properly designed experiments.

No doubt, best study of man kind is man. But there are strong ethical and legal consideration for conducting the studies on human beings. The first requirement is that before conducting the experiments on human beings, the pre-requisites of human experimentation must be met by doing the animal experiments. The present work is based on the animal experimentation.
The drugs capable of improving the muscular performance allay the sense of fatigue. No doubt under experimental conditions, fatigue can be produced in the isolated muscle nerve preparation by repeated stimulation of the muscle through nerve. The fatigue of the neuromuscular origin is perhaps important in a patient suffering from myasthenia gravis which is an uncommon disease. But in a normal man the synapse at the neuro-muscular junction perhaps never shows the phenomenon of fatigue. In a normal man the sense of fatigue probably originates or at least translated as a sense of fatigue in the C.N.S. Arthur C. Gyton (1956) writes in his text book of medical physiology; 'The nerve fibre almost never fatigues enough to block nerve transmission during normal function and only rarely does fatigue occur at the myoneural junction. However, this is definitely not true of central nervous synapses, for these fatigue very readily.' Ritchie and Nicholas, (1980) write regarding the anti-fatigue action of cocaine; 'There is no evidence that cocaine increases the intrinsic strength of muscular contraction. The relief of fatigue by cocaine seems to result from central stimulation, which masks the sense of fatigue.' Though caffein has a marked direct action on the skeletal muscle but its anti-fatigue action leading to increased
capacity for muscular work is due to its action on the C.N.S. (Rall, 1980). Similarly decreased sense of fatigue, possible improvement in physical performance and increased motor activity induced by amphetamines is due to their action on the C.N.S. (Weiner, N., 1980). Thus, the drugs either indentified by the ancient man in the fauna which are consumed in large quantities by a modern supercivilised man or synthesised by man in the chemical laboratory are having their fatigue allaying properties and possible capacity to improve physical and motor performance due to the psychomotor stimulation caused by the m at the level of the C.N.S. and not due to their direct action on the muscle or neuromuscular junction. Thus during the present studies on ephedrine work has been done to assess its capacity as a psychomotor stimulant as well as its action on the muscle, but the emphasis has been laid on the former. Dews (1953) has described the method of measuring the S.M.A. of small animals using photoelectric cell which unlike previous methods of measuring the S.M.A. e.g. by jiggle cage, can sp ecifically distinguish between the psycho- motor stimulants and other stimulants of the central nervous system. In the present studies we have used the Technophotoactoactometer which is based on the same
principle as that described by Dews to measure the S.M.A.

The actions of ephedrine have been compared with another sympathomimetic amine i.e. amphetamine which is the most extensively studied drug in military personnel and athletes as far as muscular performance is concerned (Weis and Laties, 1962). The comparison has also been made with the newly introduced drug pemoline which is supposed to have C.N.S. activity in between that of amphetamine and caffeine (Wade, 1977). Attempt has been made to elucidate the mechanism of psychomotor stimulation caused by ephedrine, amphetamine and pemoline by treating the mice receiving these drugs with agents capable of depleting and blocking the transmitters of adrenergic system because psychostimulant sympathomimetic amines e.g. amphetamine exert their actions indirectly by releasing catecholamines (Burn, 1965). The action of ephedrine and amphetamine as well as pemoline (for the purpose of comparison) has been studied on physical performance under stress using Techno Swimming test apparatus. Direct action of ephedrine on the muscle has been studied on the rectus abdominus of the frog.

As already mentioned to assess the potential of drugs under study as psychomotor stimulants their
effect on S.M.A. was measured using Techno photoactometer based on the same principle as described by Dews (1953). According to Dews (loc-cit); 'Using mice of the same strain and sex, it is not necessary to repeat the whole dose response curve for the standard drug every time such an evaluation is performed'. It was not possible to procure strain specific mice, of course some inbred mice from the animal house of the Department of Microbiology Panjab University, Chandigarh were procured. However, even the supply of these animals was very limited. Thus, under the present circumstances most of the experiments were performed on the mice supplied by the local dealer. In locally supplied mice, even the S.M.A. of normal mice varied from batch to batch. Due to this variation simultaneous studies on the control groups from all different batches supplied by the local dealer were always done and preferably simultaneous control was maintained with each set of experiments. It was absolutely impossible to make use of the S.M.A. of control group from one batch to another. Every attempt was made to control the experimental conditions. It was noticed during the present studies that S.M.A. of the control group varies with age, sex and weight and the time of the day. The experiments were performed on the adult male mice unless otherwise mentioned weighing 20-30 gm. (which is an extreme range, generally the
weight varied between 22-26 gm.). The experiments were conducted during winter months so that experiments could be carried at the most suitable and comfortable environmental temperature for the mouse i.e. 21° - 23° C. Higher temperatures prevailing during summer months in our country are likely to vitiate the results due to heat stress. As long as 200 years ago Blagden (1774, 1775) has described the harmful effects of high ambient temperature on man as well as animals.

During the course of present investigations it was observed that infant mice were more active as compared to the adults. Similarly female mice were found to be more active than the male mice. It has been noticed that there is no change in the activity from 8.00 A.M. to 8.00 P.M. when experiments are carried during winter months. Similar observation has been made by Mirsky et al (1959). However even during the early summer say in the end of April, if the room temperature is not controlled by air conditioning, the activity decreases in the noon and increases again in the evening. It was also observed during the winter months that there was sudden decrease in the activity after 10.00 P.M. Another observation which has been made during the present study is that in water deprived mice i.e. thirsty mice) activity increases very much and recently fed (both with food and water) mice become lazy.
Enhancement of S.M.A. in food deprived rats
(but given drinking water ad lib) has been reported
by Borsy et al (1960). He termed the enhanced S.M.A.
after food deprivation as orientational hypermotility.
It was observed during the present study that S.M.A.
of female mice was much more than that of the male
mice. It is interesting to note that although activity
of the female mice dwindled with time but even the
minimal activity was much more than that of maximal activity
of the male mice. The S.M.A. of female and male mice
was compared under identical experiental conditions and
groups of mice of both the sexes used for the experiment
belonged to the same batch but the fact remains that
experiment on female mice has been done on the sample
taken from the one batch only. It will be of interest
to repeat the experiments with the samples taken from
different batches to be sure that if this difference in
activity is sex related. Another chance observation
worth mentioning is that by mistake one female mouse,
presumably in oestrus, was introduced in the activity
cage along with three male mice. This group showed very
high activity approaching that of amphetamine treated
group. There is nothing unusual as far as high S.M.A.
of this batch is concerned but such a situation is of
prime importance as this would vitiate the results.
The effect of ephedrine on the S.M.A. of the mouse has been studied at various dose levels varying from 1 mg./kg. to 20 mg./kg. The dose of 1 mg./kg. given i.p. failed to produce any action in the adult male mice supplied by the local dealer as well as in the inbred mice from the animal house of the department of Microbiology, Panjab University, Chandigarh. The dose of 2 mg./kg. enhanced the S.M.A. of the inbred mice but failed to produce any action in the mice supplied by the local dealer. Again, there is difference between the influence of approximate threshold dose (2 mg./kg. in the inbred mice and 5 mg./kg. in the mice supplied by the local dealer) in the activity pattern of the mice from these two different sources. The threshold dose in the inbred mice (2 mg./kg.) increased the initial activity which reached the peak value in the 4th interval and then decreased gradually reaching the minimal activity in the last half an hour interval. The final activity being slightly less than the initial activity but definitely more than that of final activity of the control group. However, this dose of ephedrine could cause only marginal increase in the activity of inbred mice as compared to the control group. As already mentioned, ephedrine in the dose of 2 mg./kg. failed to produce any significant change in the S.M.A. of mice.
supplied by the local dealer. The threshold dose in the mice supplied by the local dealer (5 mg./kg.) always produced the decrease in the initial activity. This has been repeatedly confirmed, and decrease in activity during first half an hour interval was found to be statistically significant. Again these mice showed peak activity in the last half an hour interval and 4 out of 5 experiments the peak activity occurred in the final interval (80-90 minutes). Thus, this pattern of activity being very much different from that produced by the amphetamines. This dose of ephedrine produced increase in the total cumulative activity for 90 minutes in 4 out of 5 experiments. However, total cumulative activity for 90 minutes decreased in one experiment. Even in this experiment S.M.A. in the last half an hour interval was increased. Ephedrine induced decrease in S.M.A. during the first half an hour interval being statistically significant (P = 0.02) but enhancement of activity during last half an hour interval is statistically insignificant (Statistical analysis was done using student's t test). The experiments were conducted in 5 control and 5 ephedrine treated groups (4 mice in each group) from 5 different batches. Standard error of the mean for both control and ephedrine
treated groups was high which seems to be the major contributing factor responsible for statistical insignificance of ephedrine induced increase in S.M.A. during last interval. The sharp spurt in activity during the last half an hour interval in ephedrine treated group is so conspicuous that it cannot be ignored. Repeating the experiment in the mice of the same strain (in accordance with the original prescription of Dews, 1953) would give the more realistic picture of statistical significance. However, procurement of strain specific mice at the moment almost is practical impossibility. Dose of 10 mg./kg. of ephedrine also produced the pattern of response similar to that of 5 mg./kg. i.e. decrease in activity during the initial interval and peak response occurred in the final half an hour interval. On the other hand dose of 20 mg./kg. produced different pattern of response i.e. it produced an increase in activity during the initial interval as well as first half an hour interval which gradually increased and reached the maximum in 7th interval. The only report which we could come across on the effect of ephedrine on S.M.A. of the mouse is that of the Dews (1953). He studied the effect of various doses of ephedrine on S.M.A. (CF-1 strain of mouse) for 15 minutes. In this strain of the mouse only
dose of 1.25 mg./kg. slightly increased the activity. The next dose studied was 2.5 mg./kg. The doses of 2.5 mg./kg. up to 80 mg./kg. decreased the activity in CF-1 strain of the mouse. During the present study the effect of ephedrine on S.M.A. for 90 minutes was studied and this has revealed the dual action of ephedrine in doses of 5 mg./kg. and 10 mg./kg. i.e. there was decrease in S.M.A. during first half an hour interval and increase in S.M.A. during last half an hour interval.

Perusal of dose response curve of the paper by Dews (1953) indicate slight upward surge in activity (measured for 15 minutes) again with the dose of 20 mg./kg. but the activity remained well below the control level. During present series of experiments it has been observed that the dose of 20 mg./kg. produced definite increase in the activity above the control level in the initial interval (0 - 10 minutes) as well as in the first half an hour interval and increased activity in the ephedrine treated group continued above the control level throughout the course of experiment i.e. 90 minutes.

No reference on the mechanism of action of ephedrine on S.M.A. could be found after as thorough search of literature as could be done. Ephedrine is an indirectly acting sympathomimetic amine i.e. it acts by
releasing catecholamines (see Burn and Rand, 1962). Attempt has been made during the present study to elucidate the adrenoceptors involved in the action of ephedrine on the S.M.A. by studying its action vis-a-vis adrenergic blocking agents. Propranolol (10 mg./kg.) itself showed trend towards increasing the S.M.A. It would be logical till further experiments are done to attribute this marginal change in activity to chance or factors not related to the drug action. Alternatively, a possibility may be kept in mind only for the sake of doing further experiments, that the propranolol induced increase in S.M.A. may be due to blockade of sites of loss of catecholamines thus making larger quantities of normally released adrenergic mediators available at the receptor sites. The usual dose of propranolol generally used for blocking the beta adrenergic receptors i.e. 10 mg./kg. was used during the present study. With a relatively high dose i.e. 60 mg./kg. i.e. Barar and Nadan (1973) have reported that propranolol decreases S.M.A. in the mice.

Phenoxybenzamine which is a haloalkylamine also enhanced the S.M.A. of the mice. Other C.N.S. stimulant effects of haloalkylamines e.g. hyperventilation, motor-excitibility and even convulsions have been reported previously (Hecht and Anderson, 1947) Phenoxybenzamine decreases the food intake in animals. Thus action is quite similar to that of amphetamine, a centrally acting
sympathomimetic amines which acts by releasing catecholamines. The possibility cannot be ignored that phenoxybenzamine may be enhancing the S.M.A. by releasing or making more catecholamines available to the receptor sites in the C.N.S. regulating the S.M.A. There are two possible mechanisms; (i) Phenoxybenzamine blocks the presynaptic alpha receptors thus blocking the feed back mechanism inhibiting the presynaptic catecholamine release, this would lead to greater release of catecholamines (Langer, 1977), (ii) Phenoxybenzamine has got cocain like action i.e. it inhibits the uptake of catecholamines and in this regard it is as potent as cocaine (Cubeddu, Langer and Weiner, 1974). It is worth noting that phenoxybenzamine caused significant increase in the activity during initial 20 minutes only and finally the activity decreased. It is worth mentioning that cumulative activity for first 20 minutes as percentage of control for phenoxybenzamine comes out to be 191 per cent i.e. S.M.A. during first twenty minutes is almost double than that of the control. Experiments on phenoxybenzamine have been carried on the batch of mice which was showing steady pattern of S.M.A. Thus, the two fold increase in the S.M.A. caused by phenoxybenzamine during the first 20 minutes cannot be ignored and activity definitely decreased with time and
the activity during the last interval being only 3/4th (76.7%) of the control activity. As the S.M.A. increased during the first twenty minutes and finally it was decreased below that of the control group, it seems probable that direct action of the metabolites (as postulated for some other C.N.S. stimulating actions of phenoxybenzamine (Nickerson and Hollenberg, 1967) may not be playing major role as far as the action of phenoxybenzamine on S.M.A. is concerned. Because if the increase in S.M.A. might be due to active metabolite of phenoxybenzamine, it is expected that the activity should increase with time. Under the circumstances, it is plausible to presume that the increase in S.M.A. is mediated through the indirect adrenergic mechanisms as already postulated i.e. blockade of the presynaptic alpha adrenergic receptors and cocaine like action. Phenoxybenzamine is a well known blocking agent of postsynaptic adrenergic receptors, initially it causes reversible or equilibrium type of block and then it causes irreversible or non equilibrium type of block (Nickerson, 1949). Under the circumstances it may be further presumed that cocaine like action and of phenoxybenzamine release of catecholamines caused in the brain due to blockade of presynaptic alpha adrenergic receptors are so marked (in the areas of the brain controlling S.M.A.) enough catecholamines are made available in the synaptic cleft as to displace phenoxybenzamine
from the post synaptic receptors during the initial phase of reversible block. Subsequently as the non equilibrium type of block develops, catecholamines made available by cocaine-like action or blockade of presynaptic alpha receptors as well as those being released physiologically are not able to displace of adrenergic neurones. phenoxybenzamine from the post synaptic receptors. This might account for subsequent decrease in S.M.A. in phenoxybenzamine-treated mice. Counting of the S.M.A. was started 40 minutes after the injection of phenoxybenzamine; this time interval may not be sufficient to block the post synaptic adrenergic receptors in the brain because the drug has to cross the blood-brain barrier.

The minimal effective dose (5 mg./kg.) of ephedrine in the male mice supplied by the local dealer has been used for studying its action on S.M.A. vis-a-vis alpha adrenergic blocking agent (phenoxybenzamine) and beta adrenergic blocking agent (propranolol) as well as in the reserpine-pretreated mice which depletes the granular stores of catecholamines (Krishner, 1962). These studies have been carried in groups of mice from the same batch of animals supplied by the local dealer. As chance would have it, this happened to be the most stable group as far as S.M.A. of saline-treated animals is concerned. Apparently, both phenoxybenzamine and propranolol attenuated the ephedrine-induced depression.
in the initial activity. Both the drugs almost completely blocked the ephedrine induced increase in the peak activity, final activity, cumulative activity in the last half an hour interval and the total cumulative activity for 90 minutes. In this batch of mice ephedrine increased the S.M.A. in second half an hour interval and last half an hour interval, as well as total period of 90 minutes interval (ephedrine induced increase in S.M.A. in the last half an hour interval was more marked and more consistent).

Ephedrine in the presence of both phenoxybenzamine and propranolol decreased percentage S.C.A., percentage L.C.A., and percentage T.C.A. As already mentioned, both the blocking agents attenuated the ephedrine, induced decrease in the S.M.A. during the first half an hour interval resulting in increase in percentage F.C.A. However, the S.M.A. in the first half an hour interval of propranolol + ephedrine treated group as well as phenoxybenzamine + ephedrine treated group though greater than the ephedrine treated group yet it was much less than that of the control group. Thus, till further experiments are done, it is not possible to comment whether adrenergic blocking agents induced change in the percentage F.C.A. is due to their specific effect or merely due to chance. On the other hand
blocking action of both propranolol and phenoxybenz-
mine on ephedrine induced increase in S.M.A. in the
second and last half an hour intervals, is so marked
that S.M.A. of phenoxybenzamine + ephedrine and
propranolol + ephedrine is much less than that of even
control group. This is very interesting and challenging
observation for which it is not possible to offer an
explanation at the moment specially in view of the fact
that propranolol and phenoxybenzamine in the dosage
used during the present experiments have got the
tendency to increase the S.M.A. Another intriguing
situation is that ephedrine induced enhancement of
S.M.A. is blocked by both alpha and beta adrenergic
blocking agents. It is not possible to decode this
intriguing situation at the moment till adrenergic
receptor mechanism of the brain is delineated clearly.
Another complicating factor is that at present the
alpha adrenoceptors of vasomotor areas present in the
medulla oblongata perhaps, remains to be the only
well studied adrenergic receptors in the brain.
Phenoxybenzamine fails to block these alpha adrenergic
receptors, on the other hand these are blocked by
Yohimline is a very weak alpha adrenergic blocking
agent and phenoxybenzamine is very powerful alpha
adrenergic blocking agent as far as peripheral organs are
concerned (Nickerson and Colleir, 1975). The remarks of
Hickerson and Kollenberg (1967) who considered the brain as a 'black box' are very valid and are being reproduced below:

"It may be that adrenergic receptors in the C.N.S. differ from both of the well characterised peripheral types and that it is incorrect to assess experimental results in terms of known patterns of peripheral blockade. However, peripheral blockade is the only yard stick now available and it seems unlikely that a more accurate one will arise from observation on complex responses issuing from a 'black box'.

Another possibility which may be kept in mind is that phenoxybenzamine and propranolol may be blocking the ephedrine induced enhanced S.M.A. by acting at different sites. Cocaine like action on adrenergic mechanisms of the phenoxybenzamine has been demonstrated in the central nervous system and phenoxybenzamine is equipotent to cocaine in this report (Cubeddu et al, 1974). Propranolol has got local anaesthetic action to (Vaughan Williams, 1974) but the best of our knowledge cocaine like action of propranolol on adrenergic mechanisms in the C.N.S. has not been demonstrated so far. Moreover other local anaesthetics have not got cocaine like action on the adrenergic mechanisms i.e. blockade of uptake of catecholamines by adrenergic nerve endings (Ritchie and Cohen, 1975). Ephedrine is indirectly acting sympathomimetic amine (Burn and Rand, 1962).
It is taken up by the sympathetic nerve endings (Burn and Rand, 1962) from where it displaces the catecholamines (Burn, 1958) which are poured into the synaptic cleft when act on the post synaptic adrenergic receptors. Cocaine blocks the action of ephedrine by preventing its uptake by the sympathetic (adrenergic) nerve endings (Kaelle, G.B. 1975). Thus, the possibility is worth exploring that phenoxybenzamine may be blocking the action of ephedrine on S.M.A. (enhancement) due to cocaine like action i.e. preventing its uptake by the adrenergic nerve endings in addition to blocking the alpha adrenergic receptors and propranolol may be acting by blocking the post synaptic beta adrenergic receptors on which the catecholamines released by ephedrine may be acting, resulting in enhancement of the S.M.A. At least there is an evidence in case of tricyclic antidepressants which act by making more noradrenaline available in the synaptic cleft that their action is mediated through beta adrenergic receptors (Wolfe et al, 1978).

Reserpine pretreatment depletes almost 80 percent contents of catecholamines in various organs including brain, heart and blood vessels (Singh and Garg, 1977). Reserpine depletes the catecholamines from granules present in the nerve endings (Krishner, loc-cit) but it fails to deplete catecholamines present in the
cytoplasm of nerve endings. Psychomotor stimulant amphetamine which like ephedrine is also indirectly in acting sympathomimetic amines increases S.M.A. in reserpine pretreated animals. But pretreatment of animals by alpha methyl paratyrosine which interferes with the first step of synthesis of catecholamines which takes place in the cytoplasm does block the action of amphetamine (Wilson, Schild and Modell, 1975). Thus, the present view is that amphetamine increases the S.M.A. by releasing recently synthesised catecholamines, from the cytoplasm, which are not depleted by pretreatment of the animals with reserpine. The present studies have shown that in reserpine pretreated animals, ephedrine fails to enhance S.M.A. Simultaneous comparison with amphetamine showed that amphetamine markedly increased the S.M.A. in the reserpine treated animals as already reported by other workers (Carlson, 1970 and Von Rosson et al 1962). Thus, the present studies indicate that ephedrine and amphetamine enhance S.M.A. by releasing catecholamines from different pools. Unlike amphetamine ephedrine increases S.M.A. by releasing catecholamines from the granules present in the adrenergic nerve endings.

The action of ephedrine on S.M.A. has been compared with that of amphetamine pattern of response as well as modification of the response of amphetamine after
adrenergic blocking and depleting agents is very much different from that of ephedrine. Unlike the dual action of ephedrine on S.M.A. amphetamine causes over all uniform increase in the activity throughout the period of observation. Another difference is that unlike ephedrine, the action of amphetamine on S.M.A. is moderately reduced by propranolol but over all activity is still much more than the control group. Number of possibilities can be postulated and explored from this difference. But one of the possibility is that amphetamine increases S.M.A. through adrenergic as well as dopaminergic mechanisms in the brain (Offermeier and Potgieter, 1975) i.e. amphetamine also releases dopamine which contributes to the amphetamine induced enhancement of S.M.A. The possibility cannot be ignored that propranolol may not be blocking dopaminergic receptors mediating S.M.A. However, phenoxybenzamine completely blocked the amphetamine induced increase in the S.M.A., rather the activity of phenoxybenzamine + amphetamine treated group was less than that of control. The working hypothesis suggested for exploring the phenoxybenzamine and ephedrine interaction may be explored for phenoxybenzamine and amphetamine interaction also. As already mentioned, we have corroborated the findings of other workers (Carlson, 1970 and Von Rossum et al, 1962) that amphetamine enhances the S.M.A. in reserpine pretreated mice.
Action of pemoline on S.M.A. is different from that of both ephedrine and amphetamine. It causes two sudden sharp spurts in S.M.A. one in the first half an hour interval and second in the last half an hour interval. Propranolol blocks both spurts in pemoline induced S.M.A. Ephedrine causes spurt in activity, in last half an hour interval, which is also blocked by propranolol. Like ephedrine and amphetamine, phenoxybenzamine blocked the action of pemoline on S.M.A. In the reserpine pretreated animals after the i.p. injection of Pemoline, the first spurt in the activity was completely abolished, rather during the first half an hour interval, the animals showed no activity at all, however the second spurt in activity occurred during 40 to 80 minutes intervals.

At the moment the literature on the data regarding the action of pemoline on adrenergic neurones and adrenergic receptors is lacking, rather it is not classified as an adrenergic drug. (Wade, 1977). But on the basis of present experiments on pemoline vis-a-vis adrenergic blocking and adrenergic transmitter depleting agents it seems that pemoline enhances S.M.A. through adrenergic mechanisms. At least there is one common denominator in the action of all the three drugs studied i.e. the enhancement of S.M.A. caused by ephedrine, amphetamine and pemoline, is blocked by phenoxybenzamine
in presence of which the S.M.A. after injecting any one of these drugs is much lower than that of the control group and time response curves of combination of phenoxybenzamine with either of these three drugs become almost flat.

The action of ephedrine (5 mg./kg. and 20 mg./kg.), amphetamine (2 mg./kg.) and pemoline (10 mg./kg.) was studied on forced exercise in rats using Techno Swimming test apparatus. Practically this apparatus measures spontaneous activity under motivational stress. Activity till exhaustion was measured noting the number of revolutions of the exercise wheel on the mechanical counter of the apparatus (actually number of revolutions till animal stops activity are being noted). No doubt it is customary to consider the number of revolutions recorded as a measurement of forced exercise till exhaustion, but it is a very complex parameter. The animal may stop activity due to exhaustion or lack of motivation. Again the motivation is generated by fear complex of being drowned. The drug may modify this parameter either by altering the spontaneous activity perse or modifying the fear complex. Therefore at least four factors can be taken into account which contribute to this parameter: (i) initiative and drive for spontaneous activity (ii) stress of fear complex and motivation generated by
it (iii) appreciation of sense of fatigue or psychic reaction to sense of fatigue (iv) the limiting capacity of skeletal muscle to do exercise (As such, this parameter can be called as maximum revolutions of exercise wheel which are revealed on the mechanical counter). Under the influence of drug, the net result of modification of any one factor or combination of these factors would determine the maximum revolutions. Even the analysis of drug action on the motivation may not be possible. The motivation to continue climbing up the ribs of exercise wheel may be generated by the 'sense of pleasure' induced by the drug (so that the animal would continue the playful activity of climbing up the exercise wheel) or it may be due to enhanced fear or anxiety caused by the drug. Behaviour of the control animals makes the situation more complex. In 26 control rats (220 to 290 gm. in weight) maximum revolutions varied from 0 to 140.

Each animal was used as its own control and experiments were carried at an ideal temperature of the water for rats i.e. about 23°C. Five experiments were done with amphetamine (2 mg./kg.), six with ephedrine (5 mg./kg.), ten with ephedrine (20 mg./kg.) and five with Pemoline (10 mg./kg.). To analyse the observations, which are sum total of various complex factors and individual variation among the animals during control
experiments is of extreme degree, it would be advisable to conduct the experiments on a very large sample or alternatively conducting the experiments on strain specific animals may yield data which can be subjected to quantitative analysis as it is expected that in such animals the degree of individual variations would be minimised. Under the existing facilities it is not feasible to repeat the experiment either on very large number of animals or strain specific rats. However, certain trends emerged out of this study. Ephedrine in the dose of 5 mg./kg. decreased the activity of all the 6 rats. Range of maximum revolutions in the control group being 3 to 127 and the range of maximum revolutions after the administration of the drug being 3 to 60. Pemoline (10 mg./kg.) also decreased the activity. The range of revolutions in the control and experimental group was 4 to 90 and 0 to 73 respectively. Amphetamine (2 mg./kg. i.p.) and ephedrine 20 mg./kg. i.p.) increased the activity of those rats which were relatively sluggish (i.e. low activity in the control experiment) and decreased the activity of the active rats (i.e. high activity in the control experiments). The apparent similarity between the manifested action of usual dose of amphetamine and high dose of ephedrine may or may not be due to similar modification of basic factors, determining the activity of the animals housed in the
swimming test apparatus, rather it can be thought that modification of basic actions by usual dose of amphetamine and high dose of ephedrine may be different. It is well known fact, that amphetamine leads to sense of pleasure where as high doses and even in some cases therapeutic doses of ephedrine causes nervousness and anxiety (Ziment, 1978). This is why that traditionally ephedrine is combined with small dozes of phenobarbitone when used in the treatment of asthma. The visual observation of behaviour of animals housed in the swimming test apparatus after i.p. administration of amphetamine (2 mg./kg.) and ephedrine (20 mg./kg.) is a pointer to the dichotomy between the basic action produced by these two drugs. The amphetamine treated animals took measured steps on the ribs of the exercise wheel even though, maximum revolutions made might have been very high, each step was taken relatively leisurely giving the feeling to the observer that animals are enjoying the activity. The ephedrine treated animals took hurried steps and moved the exercise wheel ruthlessly giving the feeling to the observer that they are making an hectic effort to escape the situation. It would be interesting to repeat the experiments in an apparatus which is not provided with a wheel. The movements on whose ribs provide a very easy mode of escape.

The experiments on rectus abdominus of common Indian
frog Rana tigrina have revealed that ephedrine has got neither any direct action on this muscle nor modifies the action of acetylcholine which is a physiological chemical mediator responsible for maintaining the tone of skeletal muscles. The action of ephedrine also been studied on the rectus abdominus of the frog in the presence of EDTA as well as on the depolarised rectus muscle. It is well known that certain drugs which are in-active on the normal muscle but produce contractile response of the muscle in presence of EDTA are in a depolarised state e.g. calcium salts which have got ignorable action on the normal rat uterus stimulates the depolarised rat uterus (Edman and Schild, 1961). Similarly adrenaline produces tetanic contractions of the skeletal muscles in hypocalcaemic state (Mekerson and Innes, 1975). Both these procedures interferes with the integrity of the cell membrane. Calcium in the membrane is responsible for maintaining its stability. EDTA forms internal complex (Chelate) with calcium and removes calcium from the membrane of the muscle fibre (Tsianchi, 1968). Normally cell membrane is polarised (Negatively charged inside and postively charged outside) and naturally it cannot perform its normal functions e.g. as a barrier in a depolarised state. Ephedrine failed to contract rectus
abdominus of the frog which was exposed to EDTA before adding various doses of ephedrine. Ephedrine also got no action on the depolarised rectus abdominus of the frog.

**Concluding Remarks**

Ephedrine containing fauna remains to be one of the oldest plants used for remedial purpose and ephedrine is one of the drugs of plant origin still persisting in the modern medical armamentarium. Pages of history clearly reveal that the drugs capable of causing psychomotor stimulation have been exploited by mankind to improve physical and mental performance. The phytochemicals which are capable of increasing the muscular strength by acting on the muscle or through neuromuscular junction but are not psychomotor stimulant have never been used to improve the muscular performance. Even the synthetic drugs amphetamines, which are abused to increase the muscular performance, are well known powerful psychomotor stimulant. Thus, even the present drug abused pattern in vogue for increasing the muscular performance is in line with historically discovered pattern of drugs used for increasing the performance by psychostimulants. The use of beverages containing
psychostimulant drugs discovered in ancient times are still persisting to-day and are legally and socially acceptable e.g. caffeine containing drinks have become part and parcel of life of modern man, on the other hand synthetic drug neostigmine which causes marked stimulation of skeletal muscle (Tylor 1980) by acting on neuromuscular junction as well as the muscle has never been abused to increase the physical performance. When neostigmine was tested for any psychomotor stimulant action by the method of Dews (1953) it was found to be devoid of psychomotor stimulant action (Singh, G.S. 1981). But the chemical structure of neostigmine is such that it does not cross the blood brain barrier thus sufficient amount may not be entering the brain. Physostigmine is a drug with stimulant action on the skeletal muscle almost similar to that of neostigmine and it is able to enter the brain. Even physostigmine is not a psychomotor stimulant (Singh G.S., 1981) when tested by method of Dews (1953). Physostigmine is also not being abused for increasing the physical performance. Physostigmine is also one of the oldest drugs of plant origin which retains its place in modern therapeutics. The results of present unpublished animal experiments justifies the wisdom of ancient man who never exploited the physostigmine containing plants to enhance his mental or
physical performance. Rather the calabar beans from which physostigmine is extracted are also known as 'ordeal beans' because in ancient times the beans were once used by the native tribes of West Africa as an "ordeal poison" in trials for Witchcraft (Goodman & Gilman 1955). An interesting historical account of trial by ordeal has been given by Dragstedt (1945). Calabar beans are no more used for trials by ordeal because this use of calabar beans as an "ordeal poison" based on the intuition and impression of ancient man regarding trials by ordeal with calabar beans could not stand the test of time. But the intuitions and impressions of ancient man in picking the plants capable of increasing mental and physical performance never failed, their use could not only stand the test of time but also stringent tests of the modern laboratory and modern man has incorporated their use in his every day life.

During the present experimentation while testing ephedrine for its 'psychomotor stimulant' properties by the method of Dews (1953) the drug was found to be having dual action. In the initial half an hour interval it decreases the activity and in the last half an hour interval it increases the activity. To analyse the data statistically the experiment with the minimal effective dose (5 mg./kg.) causing obvious alteration in the
activity of the mice have been repeated in five groups of 4 mice each from different batches. It may be mentioned that dose of 5 mg./kg. of ephedrine is relatively high dose for the mice. Simultaneous, five control experiments were done using the same number of animals in each group. The statistical analysis of the data that of these 40 mice revealed under the influence of ephedrine, decrease in activity during initial half an hour interval is statistically highly significant, but increase in activity during last half an hour interval is statistically insignificant. The spurt in activity during last half an hour interval is obvious that it cannot be ignored. In view of large standard error of the mean of the control and drug treated groups, to find the more realistic statistical significant, it will be worthwhile either to repeat the experiments in the inbred animals of the same strain or to use larger number of animals. We had already used 40 animals to study the effect of single dose of ephedrine and using still larger number of animals is not economically viable proposition and procurement of inbred animals of strain specific mice is practically impossible. But any how the situation is obvious that ephedrine induced decrease in activity is clearcut, whereas ephedrine induced increase in activity is marginal.
Thus, present experiments testify the wisdom of ancient man who did not pick up the ephedrine containing plants to increase physical and mental performance. On the other hand not only his wisdom in picking up the fauna capable of increasing mental and physical performance never failed but he also passed on the 'pick of his choice' to the next generation and the generations after generations tested them and confirmed the effect so that their use persisted till to-day.

So, taking into consideration the history of fauna capable of increasing the physical performance and the results of the present experiments on S.M.A. it is unlikely that ephedrine can improve the performance of athletes and other sportmen. Moreover when action of ephedrine was tested on spontaneous activity of rats under stress (forced exercise) the dose of 5 mg./kg. decreased the activity of all the animals tested. The dose of 20 mg./kg. of ephedrine (practically a toxic dose) increased the activity of rats having low activity in the control experiment i.e. inactive rats, but decrease the activity of rats having high activity in the control experiment i.e. active rats. It need not be mentioned that athletes/sportsmen represent the most active sample of human population as far as muscular performance is concerned and they are always under stress during competition.
On the other hand there is no doubt that anxiety and nervousness are the established side effects of ephedrine. It is so well known that anxiety hampers the performance of sportsmen and these days active research is in progress to devise the ways and means to allay the anxiety of sportsmen (Dishman, 1980; Feltz and Landers, 1980). Thus the possibility cannot be ignored that ephedrine by inducing or increasing anxiety may even decrease the performance in sports. Caffein diet increase the physical performance (Weis and Laties 1962) and one cup of coffee contains sufficient amount of caffein (about 100 mg.) as to produce its affect on physical performance. Coffee and other caffein containing drinks are part and parcel of every day diet of modern man and it is improbable that their use can be eliminated during the sports (Van Handel, 1980). Under the circumstances, thus, it is felt that valid medical use of ephedrine should not be banned during athletics and other sports competitions.