CHEMICAL AND PHARMACOLOGICAL CHARACTERISATION OF SOME TRADITIONAL REMEDIES USED BY BOMOH'S IN THE MANAGEMENT OF DRUG ADDICTION

A DISSERTATION

by

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TABLE OF CONTENTS:

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ABSTRACT:

- In the present investigations, the samples obtained from Bomohs were examined for their properties which were claimed that can be used in the management of narcotic addiction. These were studied from various aspects of the narcotic addiction in the mice. All together six samples were studied and were labelled as Sample I, Sample II, Sample III, Sample IV, Sample V and Sample V

- Morphine tolarence in mice were induced by a single-dose as described by Jacob J.J. et. al., (1972, 1974). The precipitated withdrawal syndromes were induced using nalorphine, the narcotic antagonist.

- Both samples I and II are able to supress the precipitated withdrawal jumping in mice and the most probable pathways are via dopaminergic system.

The rest of the samples are not able to supress the precipitated withdrawal jumping in mice.

- Analgesia property of the samples are evaluated using the modified hot plate method. This assessment are based on the reaction time shown by the mice. The results indicated that the analgesia properties of the samples are varies from one to another. Sample I has longer time of the analgesia property of morphine, Samples II and III about the same of analgesia time of morphine,

Samples IV and V having shorter analgesia time compared to morphine, and Sample VI has less or no effect on analgesia time of morphine.

- General behaviours of the mice treated with the samples also examined. This make use of hole-board test whereby the number of crossings, the number of dippings and the number of preens were evaluated. Besides this, the spontaneous motor activity also assessed using the animex activity meter.

All the samples tested are capable of increasing the exploratory behaviours which were lowered by the morphine. The spontaneous motor activity on the other hand, were decreased in the presence of these samples. Thus, the raising in spontaneous motor activity caused by morphine will be decreased by all the samples.

- Body (rectal) temperature of the mice were examined using the tele-thermometer. Morphine will cause the lowering of the body temperature. On examination of the samples - all of them are capable of increasing the body temperature of the mice.

- All the samples also elevated the respiratory depression caused by the morphine. The state of alertness and irritability also increase in the presence of all these samples.

- None of the samples contain opiates, tropane alkaloid, rowalfia alkaloid (reserpine), ergotamine and yohimbine.

1. INTRODUCTION:

Drug abuse especially narcotic type of drug is currently viewed as a worldwide problem and this deleterious effects lead to drug addiction whereby dependency and tolarence developed. According to World Health Organisa tion (WHO) definition, 1957 - Drug Addiction is a state of periodic or chronic intoxication produced by the repeated consumption of a drug (natural or synthetic).Its characteristic include:

- an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means.
- a tendency to increase the dose.
- a psychic (psychological) and generally a physical dependence on the effects of the drug.
- detrimental effect on the individual and the society.

The disturbance i.e. withdrawal or abstinence syndromes are made up of specific arrays of symptoms and signs of physical and psychic nature that are characteristic for each drug type - Eddy et. al., 1965

If one get 'hooked' to specific drug, the dependency then developed. According to WHO definition, 1969 - Drug Dependence is a state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioral and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects and sometimes to avoid discomfort of its absence. Tolerence may or may not develop and one person may dependent on more

than one drug.

The WHO also defined some other terms related to the drug dependence and tolerance.

- Physical dependence is an adaptive state that manifests itself by intense physical disturbances when the administration of the drug is suspended or when its action is affected by the administration of a specific antagonist.

- Psychic dependence as the intense craving and compulsive pertuation of abuse to repeat the desired effect of a drug.

- Tolerance as the phenomenon of dose increase to maintain the drug effect.

Narcotic drugs such as morphine, heroin and their derivatives lead to dependence all have in common the property of producing a rapid hightening of mood, or reduction of tension, followed by a feeling of 'let-down', which in turn can only be relieved by taking more of the same drug.

Treatment of the drug addiction is not that simple. It involved the treatment of the physical as well as the physiological of the drug addicts. Beside this the period of treatment may extends for a long period of time. Several attempts have been made to improve the treatment, but the effectiveness of thet still being questionable. Although there are so many methods of treatments available, the basic conceptualization of treatment technique employed by modern medicine involved the following procedures.

Heroin maintenance ⟶ Methadone maintenance ⟶

Apomorphine ⟶ Propnalol ⟶

Acupunture ⟶ Electrosleep ⟶ Biofeedback ⟶

Hypnosis ⟶ Meditation

In Malaysia, beside modern treatment available in the Drug Rehabilitation Centre and other form of modern modalities employed, the role of Traditional Healers or 'Bomoh' so far can be considered one of the method which help to treat drug addicts. There is evidenc that some drug addicts in Malaysia has turned to the traditional healers, particularly Malay Bomoh for assistance in the treatment of their narcotic addiction. Although not much work has been done on Bomoh, the one which initiated and studied by Kris Heggenhugen show that the Bomoh in some way or another help to cure the drug addicts in order to 'kick-out' their habits.

1.1. Review on precipitated withdrawal (abstinence) syndromes:

Since the major part of this investigation involved the use of precipitated withdrawal syndrome as the 'main model' and also for testing the Bomohs' Samples, it is deemed important and necessa ry to get a general review of this phenomenon.

The morphine abstinence syndrome or withdrawal reaction is precipitated by any termination of morphine administration or by injection of antagonist. From this point of view, the whole series of this investigation make use of Morphine Antagonist.

Morphine antagonists are compounds which block or reverse the agonistic effect of the opiates (morphine). Clinical application as an 'antidote' for acute narcotic intoxication by reversing narcotic depressant effects and for treatment of addiction by blocking the effect of self-administration of narcotic. The pharmacological effect of narcotic-narcotic antagonist combination depends on the compound which are used, ratio of the sequence and the route of their administration.

For this purpose in this investigation, the morphine antagonist used is Nalorphine - that is Nalorphine hydrobromide Injection B.P., under the tradename Lethidrone. The morphine addiction is induced by a single dose injection of morphine.

Many investigators have attempted to explain the abstinence phenomenon by implicating the interactions between narcotic drugs and the proposed 'neurohumoral transmitters' or 'modifier', for example Serotonin, Noradrenalin, Dopamine, Prostaglandin and Acetylcholine.(Way et. al., 1968; Schwartz and Eidelberg, 1970; Collier et. al., 1972; Pinsky et. al., 1973; Ho et. al., 1973). Interaction between morphine (and related agents) and acetylcholine have becoming increasingly implicated, but the findings in some respects have been confusing and apparently contradictory (Grumbach, 1969; Crossland, 1970; Fuentes, 1970; Frederickson, 1971; Pinsky et. al., 1973; Collier et. al., 1972; Wei et. al., 1972; Bhargava and Way, 1972). It is generally agreed that morphine and related agents acutely inhibit the release of acetylcholine from various sites (Paton, 1957; Schaumann, 1957; Frederickson and Pinsky, 1971; Belesin and Polak, 1965; Sharkawi and Schulman, 1969; Jhamandas et. al., 1971), and it has been postulated that the withdrawal syndrome could result from excessive release of accumulated acetylcholine stores onto supersensitive receptors (Paton, 1963, 1969; Collier, 1965, 1968, 1969; Pinsky et. al., 1973). Attempts at modifying the withdrawal phenomenon with cholinergic drugs, however, have not always produced results constantly consistent with the postulation. Fuentes, 1970 reported that physostigmine increase and atropine lessens the severity of the morphine withdrawal syndrome in rats while Grumbach, 1969 reported that opposite effects. Rhamken, 1968 claimed that 'cholino-

lytics' provided relief from withdrawal stress in human. Collier et. al., 1972 found biphasic effects of treatment with atropine withdrawal precipitated by naloxone in rats. Frederickson, 1971 and Pinsky et. al., 1973 found similiar biphasic effect with atropine , mecamylamine and their combination on the morphine abstinence syndrome in rats. The same anticholinergic drugs were found to diminish response to naloxone-precipitated morphine withdrawal in mice (Jhamandas and Dickinson, 1973) and to attenuate the severity of autonomic upset in rats undergoing naloxone-precipitated withdrawal (Jhamandas et. al., 1973).

It appeared worthwhile to examine the role of 5-hydroxytryptamine (5-HT, serotonin) in the genesis of morphine tolerance and dependence. Molecular models of morphine and 5-HT exhibit some degree of complementariness, and the two compounds appear to be antagonistic with respect to their effects in the peripheral (Medakovic 1959); Gyermek and Bindler, 1962; Kosterlitz and Lees, 1964) and central nervous systems (Gaddum and Vogt, 1956). The administration of 5-HT or its metabollic precursors attenuated the abstinence syndrome (Huidobro et. al., 1963). Collier, 1965 proposed that an adaptive increase in the supply of receptors for a particular neurohormone may occur if morphine acts either by reducing levels of an excitatory transmitter or occupying the receptor sites. Among the several neurohormone he considered which might oppose morphine, Collier mentioned 5-HT, and he also pointed out that the central effects of 5-HT precursor, 5-hydroxytryptophan, are similiar in certain

respects to the abstinence syndrome.

Several reports said that brain levels of 5-HT in the rats and dogs remain unchanged after long-term morphine treatment (Cochin and Axelrod, 1959; Gunne, 1963; Maynert et. al., 1962; Sloan et. al., 1963). Such measurement reflects essentially the steady-state level of brain 5-HT resulting from equal rates of synthesis and efflux, and conceivably, the dynamic aspects of 5-HT metabolism could have been altered without necessarily affecting its net concentration in the central nervous system. A comparison of the rate of brain turn-over of 5-HT between tolerant and non-tolerant mice indicated that tolerance and dependence to morphine was accompanied by an increased rate of brain 5-HT (Way et. al., 1968), the present study confirms and extends these findings.

The role of catecholamine as central transmitter in the morphine withdrawal syndrome has been the subject of a series of investigations (reviews by Collier, 1973 and Way, 1973). The results concerning the catecholamine are very contradictory. On the other hand, catecholamine are supposed to protect from morphine withdrawal (Matilla et. al., 1968), while on the other hand, central catecholamine are assumed to be essential for the full expression of the abstinence syndrome (Maruyama and Takemori, 1973). In some of the genesis of the spinal cord signs of withdrawal catecholamine seem to play no role (Martin et. al.,1967). Reports on inhibition of abstinence signs by amphetamine (Hoffmeister and Schlichting, 1972; Kamei et. al., 1973), cocaine (Hoffmeister and Schlichting, 1973), amitryptiline (Kamei et. al., 1973), L-Dopa (Huidobro et. al., 1963),

pargyline (Altenburg and Kuschinsky, 1971) and iproniazide (Maggiolo and Huidobro, 1962) are difficult to reconcile with other data (Schwartz and Eidelberg, 1970; Maruyama and Takemori, 1973; Bhargawa et. al., 1972; Pozuelo and Kerr, 1972) indicating that inhibition of catecholamine synthesis diminishes withdrawal intensity or at least some signs of it.

On the other hand, other authors after inhibition of catecholaminergic mechanisms observed no effects on withdrawal in rats (Gunne et. al., 1969) and monkeys (Segal et. al., 1972) or even an increase of some withdrawal signs in dogs (Gunne, 1965). Enhanced precipitated withdrawal was foune in mice after pretreatment with 6-hydroxydopamine, a drug which induces degeneration of catecholamine-nerve terminals (Friedler et. al., 1972). One reason for such discrepancies might be that in the various investigations different withdrawal signs were considered. While in mice jumping was usually evaluated the results obtained in rats were based on a series of signs. The ranking of impertance of which varied from author to author. Morever, withdrawal was precipitated in animals that had developed quite different degrees of dependence, which might be another reason for the contradictory results.

As far as we can see from above investigations, the morphine abstinence syndrome are related to the biochemical-changes and also to neuroanatomical areas taking place in the brain or rather in the central nervous system.

On the physical view, the most characteristic figure, precipitated abstinence syndrome in mice characterised by defeacation, urination, increased motor activity and exploratory behavior, tremors, sometimes convulsion and the most characteristically by 'stereotyped jumping' (Way, Leong and Shen, 1969). The withdrawal syndrome seen in narcotic addiction is believed to be a counter adaptive response to the effects of frequent repeated administration of high dose of the narcotic drug over prolong period of time. The body in general and especially the central nervous system has developed an adaptive beside being induced by the narcotic drug to maintain its homeostasis, and thus, suddenly withdrawal narcotic drug will results in a state of latent hyperexcitibitity. These will then give all sorts of withdrawal syndrome either related to psychologically or even to physiologically.

1.2. Narcotic addiction treatment modalities as practised by Bomohs:

There is not the same way the Bomohs used to treat their patients. There is no standardization but similiarities can be observed. All Bomohs use one or more medicinal 'teas' during the detoxification phase. Such concoctions are given regularly for periods which vary from only three days to periods which extends as long as one to three months. Since the majority of the Bomohs are Muslim in religion, as part of their treatments programmes a spiritual components are included, which involved the incantations from the 'Holy Koran' as well as religious teaching sessions and the incultation of regular prayers and the reading from the 'Holy Koran' verses. Some Bomohs perform special 'hatred charms' (pembenci) against the narcotic drugs and also give some cleansing baths and massages.

Also the Bomohs unwilling to reveal the exact ingredien of their medicinal concoctions. These concoctions appear to vary from simple mixture to extremely complex ones. The most they said is, it contains a components of herbal leaves, roots and tubers. These shown that their methods and the way they prepared these concoctions are closely guarded secrets.

Besides that, some concoctions also given to the patients in order to 'strenghtening the bones of the body' and makin the body to 'regain proper oxygen flow'. In addition, some type of 'oily mixtures' also given for gastric pain and also to assist in restoration of appetite and also for strengtening the body on the whole.

1.3. **Bomohs' Samples Investigated:**

SAMPLE I - Sample I was obtained from Bomoh Radin Suratman, of Datuk Keramat, Kuala Lumpur.

- it is a brownish colour solution, containing dissolved particles and it is non-smelly (odourless).

SAMPLES II, III, IV, V and VI - were obtained from Bomoh Norizan of Segambut Dalam, Selangor.

SAMPLE II - a dirty pale black suspension, whereby fine particled suspended in the solution. Known as 'Triphola Churna', and to be drunk by the addicts.

SAMPLE III - a dark black solution without suspended particles. Known as 'Ubat Air Barkath' and it was claimed to be aiding the digestion of the stomach. To be used during detoxification period as drinking water.

SAMPLE IV - a semi-solid form, black in colour with an oily layer. Known as 'Basmah Air', and to be drunk by the patients.

SAMPLE V - is a black semi-solid form. Known as 'Mahjun Akali', it was claimed to be useful to increase the appetite of the patients undergone treatment.

SAMPLE VI - it is a powder form with some small and coarse particles. Known as 'Serbuk Kari' (curry powder) and to dissolve in water. To be used as drinking water. It is yellow in colour.

2. PHARMACOLOGICAL INVESTIGATIONS:

2.1. Quantitative methods for measurement of narcotic abstinence:

The procedure employed to produce the single-dose tolerance in mice during this investigations are as described by J.J.C. Jacob et. al., 1974.

Nalorphine, the narcotic antagonist is used in order to precipitated the abstinence syndrome in the tested animals, which were mice. By giving this antagonist to the mice, the narcotic tolerance will be reversed and the most characteristic phenomenon observed during this withdrawal syndrome is the 'stereotyped jumping' shown by the mice.

The jump is defined as the response shown by the mice in which all its paws are off the ground at the same time. The number of jumps made by the mice after administration of the antagonist is used as a measure of the withdrawal syndrome. This single-dose method in some specific condition potentially valid for quantitative comparisons of potencies of the antagonist in precipitating abstinence and preventing it.

Beside this, the effect of Bomohs' Samples on this precipitated withdrawal jumping also investigated. This to evaluate the effectiveness of the samples block the precipitated withdrawal jumping whereby can be used in treatment of drug addicti

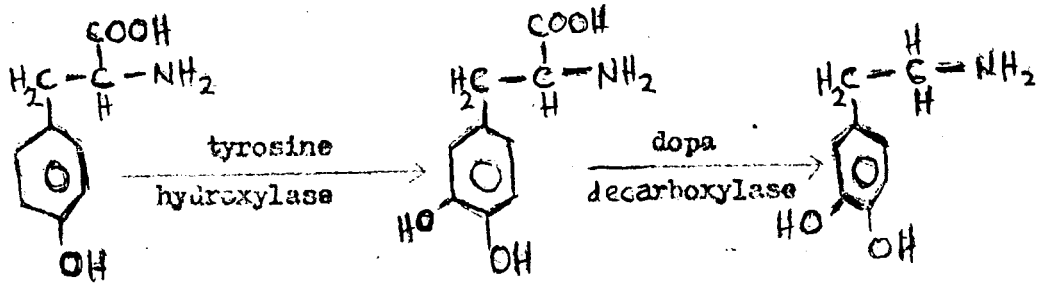
Also investigated in this area, is the presence of Brain Modifying Amines which will affect the precipitated withdrawal jumping shown by the mice in respect of stereotyped jumping. Further investigations included the administration of Bomohs' Samples in the presence/the brain modifying amines. / of

Brain Modifying Amines used:

i) L-3,4-dihydroxyphenylalanine (L-Dopa).

L-Dopa is a precursor of dopamine. The precursor is used instead of the dopamine itself since dopamine if injected parenterally is not able to cross the blood brain barrier because it is too polar. By injecting L-Dopa, the brain content of dopamine will then increased. Dopamine is suggested to be an adrenergic transmitter of the catecholamine-type in the central nervous system. Dopamine has all necessary characteristics to merit its consideration as a neurotransmitter and its neurological activity is specific to certain brain structures such as extrapyramidal system and corpora striata (Sourkes and Poirier, 1968).

The syntesis of dopamine follows the pathways as shown below:



TYROSINE DOPA DOPAMINE

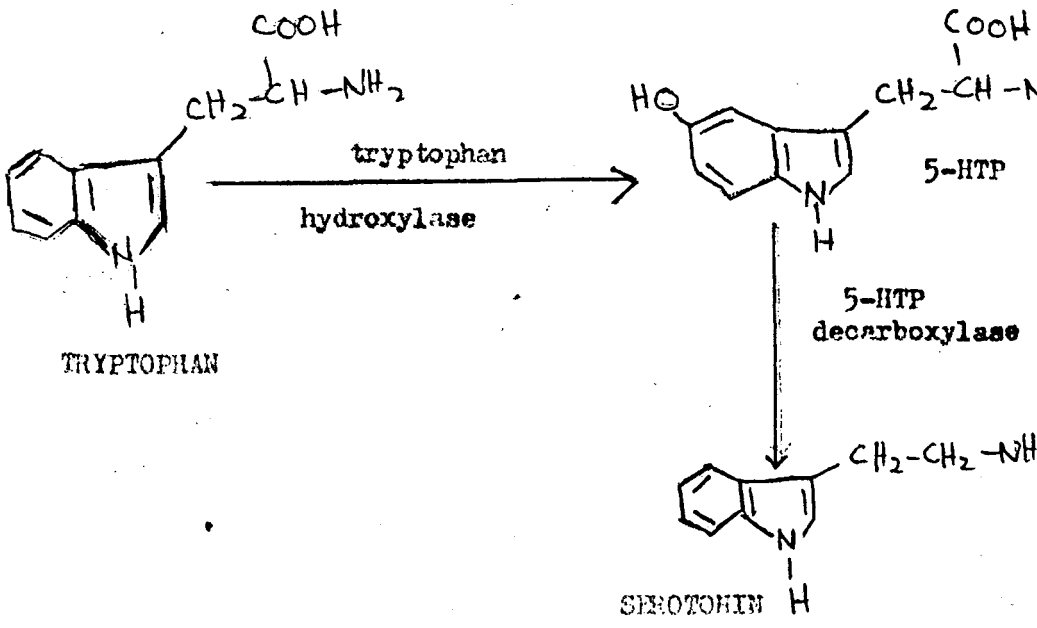
ii) α-methyl-para-tyrosine(α-MPT).

α-MPT is the depletor of the brain dopamine, and also deplete the noradrenaline content of the brain. This effect is seen in almost animals species.

Its action in respect the depletion is by inhibiting the rate limiting enzymes tyrosine hydroxylase and subsequently inhibits the formation of dopamine and noradrenaline. An investigator Spector at al., suggested that α-MPT decreases the catecholamine level in the brem stem and the caudate nucleus. However, a single dose of α-MPT is not expected to lower the noradrenaline content levels appreciably.

iii) 5-hydroxytryptophan (5-HTP).

5-HTP is a precursor of the serotonin (5-hydroxy-tryptamine). It is given to increase the serotonin levels in the brain. The pathways of the synthesis is shown below:



iv) Para-chlorophenylalanine (PCPA).

PCPA is a potent depletor of serotonin in the experimental animals. Koe and Weissman, 1966 reported that PCPA is able to lower brain catecholamines but serotonin levels are far more drastically reduced. PCPA can deplete total brain serotonin to 10% or less of the normal values and the concentration remains at this level for a few days after drug administration and slowly returns to normal level over a time of ten days. PCPA is thought to inhibit serotonin synthesis by blocking the enzyme tryptophan hydroxylase. The hydroxylation step is the rate limiting step in serotonin synthesis, hence the synthesis of serotonin is markedly reduced.

2.2. Technique for evaluation of analgetic drugs in animals:

Analgetics are compounds which allay pain. Pain can be considered as a response to a noxious stimuli which results in a state of discomfort of the organism or animals. This discomfort can be graded from mild to agony.

All of the Bomohs' Samples are tested for their analgesic properties. Thesa samples are injected to the tested animals, i.e. mice and their analgesic properties are evaluated.

There are several methods for the assessment of the analgesia testing. They are divided into heat, pressure, chemical or electrical method. Whatever methods are used, some criteria are necessary in order to test this analgesia properties. Goetzl et. al., 1943 described a series of criteria which are necessary for a useful test procedure:

- permit quantitative determination of threshold values of stimuli.

- build information on at least discernible differences between the intensities of two stimuli at every point within the range of useful intensities.

- be applicable to both man and animal.

- if different qualities of pain exists - the analgesimetric methods should quantitatively determine each quality.

Heat, pressure and electricity as analgetic stimuli are almost exclusively directed towards the evaluation of the narcotic analgetic activity.

For its simplicity, the heat (thermal) method was used for this purpose. Hea t method has been extensively used for the analgesia testing. The first investigators using the heat method are Woolfe and Mc Donald, 1944 - where the used or 'hot-plate' method is introduced. Begin on this heat method, some other modification has been done by Eddy Leimbach, 1953 and by Grotto and Sulman, 1967 - where they made use of hat-plate method with modifications.

For purpose of this investigation, where Bomohs Samples are tested for their analgesic properties, the hot-plate with modifications was used. The test animals are subjected to thermal stimulation by placing them in a metallic cylinder in which was placed in water-bath maintained at 55 $\pm$ 1°C. The reaction time is based by the time the mice try to lick its hind paws of by jumping out of the cylinder. The exposure time was limited to up two minutes in order to avoid tissue damage.

2.3. Evaluation of spontaneous motor activity:

Several techniques for measurement of spontaneous motor activity or, more briefly, the spontaneous locomotor activity of small animals have been described. As employed by Steward in 1898, the devise known as revolving drum, or activity wheel was used. This method essentially consists of a centrally pivoted drum-shaped cage in which the animals is placed so that its gross movements are transformed by the drum into revolving motions that are counted within a specified interval of time. The main drawback of this method is that very minimal movements cannot be recorded and also suitable for measurement of drug-induced rather than increase of motor activity.

Ritchie, 1927 has described and employed another method, designated as the 'swinging cage', this consists of a cage resting upon pneumatic sockets connected by tubes to a pen writing on smoked paper. Wilbur, 1936 and Hunt, 1939 proposed some minor variations of this apparatus, mainly consisting of a spring system on which a cage was suspended to allow for swinging to be initiated by the movement within the cage. In contrast to the rotating drum, the swinging cage is very efficient for recording and measurement small animal movements and tremors, but it is quite unsuitable for the careful measurement of extensive gross movements.

For this purpose, new apparatus was used. It is based upon a series of electromagnetic fields which are modified by the animal's passage within them. This system, completed by a counter and a timer, it is quite sensitive and contain no 'dead-ground'; however, it cannot record tremor in small animals, which is often an important aspect of locomotor capacity. This apparatus known as Animex Activity Meter.

From a general point of view, the ideal apparatus for the measurement of spontaneous locomotor activity must have the following characteristics:

- sensitive to every type of animal movements.

- sensitive to the slightest changes in the animal's activity and movements.

- without any dead-ground in its functioning.

- constant in its function.

2.4. Quantitative methods in testing the exploratory behaviour:

The samples taken from Bomoha also tested for its effect on the mice on its exploratory behaviour.

Exploratory or orienting reflexes, essentially consists of a response made by an animal to novel or unanticipated stimulus; the response involves cessation of ongoing activity with an attentional shift to the stimulus source. Such a reflex is characterized by the fact that, if the frequency of the stimulus presentation is increased within a brief interval, the orienting response gradually disappears. The response may reappear if the stimulus is represented, for instance, or the following day, but, after a series of subsequent reinforcement and extinctions, the response permenently fades (Berlyne, 1960) as it gradually loses its properties of uniqueness or novelty.

On the same basis, a rat is more inclined to maintain interest in an object or situation that has not previously been experienced in the experimental situation than in some conditions just explored within the previous ten minutes (Bernine, 1950); similiarly, an animal maintained in a new environment develops a mode of behaviour orientation towards exploration of the characteristics of such an environment. Also in this case, the exploratopy, or orienting reflex diminishes and tends to disappear when the experimental situation is repeated in time (Berlyne, 1950; Montgomary, 1953).

It also seem clear that, exploratory behaviour is based upon a series of central activities, among which emotionality plays a prominent role. In fact, all of those factors capable of leading to increase in the arousal level, such as painful, fear, range, noise, distraction from an exploratory task, etc., tend to render both man and animals less inclined to become aware of the novelty or complexity of the stimulus (Chapman and Levy, 1957; Hayward, 1963; Thompson and Higgins, 1958).

In this investigation, the method employed is adopted by Boissier and Simon, 1962. 1964 . This method is known as hole-board test, the most useful set-up to study animal behaviour in a free environment.

The measure of activity is represented by the number of holes explored by the mice by inserting its head into the holes in specific time. The control mice recorded to be compared with the treated mice. Beside this, the number of crossing made by the mice on the hole-board also recorded.

Having done these investigations, the results will give some explanations about the exploratory behaviour of the mice after being treated with the Bomoha' Samples.

3. CHEMICAL INVESTIGATIONS:

The samples obtained from Bomohs are tested for the presence of alkaloids. As mentioned earlier, in Introduction part, the concoctions prepared by Bomohs are varies from simple to extremely complex mixtures. Most of these prepared from herbal leaves, roots and tubers. Thus, the main sources are the plants. This investigations, try to identify the alkaloids content.

Before this, a general reviews abour alkaloids are deemed important in order to understand the subjects.

3.1. General characteristics and properties of alkaloids.

The chemistry of alkaloids become more interesting subjects since the isolation of morphine by Sertuner, 1817. Since that, several hundred alkaloids have been isolated from various plants and chemical constitutions for many of these have been elicudated. Thousands of different plants species have been investigated within the past two decades for the alkaloidal constituents. However, only a relatively small number among all known alkaloids are currently of importance from the therapeutic or pharmacological point of view.

The alkaloids have been traditionally treated as a 'group', and yet there has been no statisfactory definition of an alkaloid. This is so, because the term alkaloid is not a chemical designation but rather a name traditionally and accepted for a group of nitrogen-containing, basic substance from plants with rather

widely different chemical constitutions. Neverthless, there are several common features and attributes, which, to a greater or lesser degree, are associated with or possessed by the compounds known alkaloids, cases of exceptions to one or more of these features can be cited. The features are as followed:

- alkaloids are more or less compounds produced by plants.

- they contain nitrogen in the molecules.

- many, probably most, alkaloids are derived, in their biosynthesis, at least partly from various amino acid as their direct precursor.

- they are basic (alkaline) in reaction.

- they are usually soluble in number of immisible organic solvents, butrather insoluble in water.

- many of them are pricipitated by certain reagents.

- a number of them give more or less characteristic colour reaction with certain reagents.

- most of them are susceptible to destruction by heat; a number of them undergo decomposition or degradation by exposure to air and/or light.

- a great number of alkaloids show pronounced pharmacological actions on various organs and tissues of man and animals.

4. EXPERIMENTALS:

4.1. Experimental animals and environment.

Mice used throughout this study are obtained from animal house of School of Pharmacy, Universiti Sains Malaysia. They were weighing between 25 to 30 grammes. They were fed on food pellets and water ad libitum. The experiments were done in the Pharmacology Laboratory and the room temperature is 25 ± 1°C.

4.2. Drugs and routes of administration.

Morphine - Morphine sulphate B.P. (May and Baker) in powder form. 200 mg. of powder is dissolved into saline. The volume was made up to 10 ml. The stock solution containing 20 mg/ml of morphine sulphate.
Dose administered 100 mg/kg s.c.

Nalorphine - Nalorphine hydrobromide injection under tradename Lethidrone (Burrough Wellcome & Co.). 1 ml. ampoule containing 10 mg/ml.
Dose administered 75 mg/kg i.p.

L-Dopa - L-β-3,4-dihydroxyphenylalanine powder (Sigma Chemical Co.). 300 mg. was dissolved in few drops of conc. HCl volume was made up to 10 ml. with saline.
Dose administered 300 mg/kg i.p.