SCREENING AND IDENTIFICATION OF UNKNOV7N i DRUG (CMP IIT)

BY

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A dissertation submitted in partial fulfilment for the attainment of the degree of Bachelor of Pharmacy

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"It is important to explore many testing procedures and test conditions: the continuing examination of a possible new test procedure should be a part of each major program of drug testing"

ACKNOWLEDGEMENT

I am most grateful to my Supervisor, Dr. Gichuru Muriuki for the invaluable help and guidance. I also do wish to thank all technical staff in the section of Pharmacology including the chief technician Mr. D. K. Njoroge, Mrs. Munenge and Mr. Wangai without whose help this piece of work could not have been.

My thanks also due to Dr. Hensah's help and for extracting and supplying the compound.

Also special thanks go to Kitosh for lubricating the throat whenever convinient or conditions allow.

I also can't forget to thank my classmates for appointing me and re-electing me the class representative for the four years.

And lastly but not least thanks go to
for typing the manuscript.

DEDICATION

This piece of work is dedicated to my late Father, Ben Ndivo. Also to my Mother, Anna Ndivo, my wife Perpetua, Brothers and those friends whose both moral and material support contributed to the sucess of this work.

TABLE OF CONTENTS

ABSTRACT

Purpose of this Project was to carry out Pharmacological screening of an unknown'compound CMP IIT extracted from the Croton species plant. This# compound is a whitish powder with no characteristic smell. It is insoluble in water. Therefore, the formulation of the suspension for intrapentoneal injection to mice was done by first infrating the powder with certain amount of tragacantLto make a solution of 10% W/V trangacanth.

Although this compound was soluble in other organic solvents like ethanol and acetic acid, these two solvents could not be used as a vehicle because they will also display their own effects hence making it difficult to interprete the observations.

This compound CMP IIT had several pharmacological activities, but out of the ones outlined in the discussion, only those which were of interest were studied in detail. These included:

L. The effect of CMP IIT on the blood pressure of a rat. Here, this compound was found to lower the blood pressure of a rat, and the systoli<I pressure was the one affected most. Since there are several ways in which a compound or a drug can lower the blood pressure, the exact mechanism of action is not known.

. The compound had also some profound effects on the central nervous system. The sedative feffect of this compound was compared to that of known sedative hypnotic i.e. pentobarbitane, but was found that, it was not better.

This compound CMP IIT had also anticonvulsant activity. Since when injected together with a central nervous stimulating drug which cause convulsions, i.e Bemcgride.—The mice never died out of convulsions, although initially the convulsions are observed but, after some time, which I think is time taken by drug to reach brain, it counteracts the Bemegride—induced convulsions.

IHTRODUCTION

Combating diseases with drugs is a timeless strug§e. Its beginnings echoed out of the primeval jungle. Han's survival on this planet has depended upon his success. Today the conflict continues unabated in Chemistry Laboratories and hospital clinics. The scientific approach to this struggle is Pharmacology.

The screening of synthetic and natural products is being performed on a vast scale. This is mainly carried out in Fharmacology Laboratories.

The term screening indicates the use of a combination of tests for the purpose of making a decision. The results of the tests provide information on the presence of certain pharmacological properties. A decision whether the tested substance should be studied further may be founded on that information. Incidentally the direction of further study may also be determined by this information.

The operation of retaining from a group of substances those possessing a certain property is fundamental. Screening is the most efficient method of detection and of decision-making in any empirical operation. The finding of substances with a pharmacological property with molecular structure exists.
The screening of drugs involves scanning and evaluation. The scanning always involves a test or a group of tests which, it is believed, will permit the detection of physiological activity.

The main screening method adopted in this project is blind screening. Blind screening is carried out if a new series of chemical substances becomes available, either through isolation from a natural source or through synthesis, there may be no information on its pharmacological activity in Literature. The blind screening provides clues to potential activity, at least, and preferably, to indicate fields of activity if they,exist. In addition, the blind screening ought to show pharmacological inertness if it exists. The :hief

purpose of the screening are to demonstrate whether the new compound sr group of compounds is worthy of further attention and to indicate which snong them have the most interesting pharmacological properties.
3lind screening, the technique for detecting pharmacological activity in a substance or group of substances, without pharmacological•history* requires considerable planning and skilled execution of the tests, in order to be

be economical of time and money. The strategy of a few test, having simple procedure, to be applied to cheap animals, requires a knowledge of the tests that are known as well as ingenuity in their combination screening is essentially a scanning procedure designed to distinguish useful from non-useful drugs as rapidly comprehensively and inexpensively as possible.

In blind screening the best approach is one where no assumptions are made about what the probable actions of a compound may be, except when an already carefully studied series of compounds having similar structures has been investigated. In order to decide quickly whether a substance is worthy of further study, it is best to proceed from the general observations to the specific and from comprehensive observational techniques to the use of instruments. Many researchers in Pharmacology at times fail to recognise the importance of observing the animal's gross behaviour, as a quantitative method. A standardised, carefully defined procedure may provide data of as much reliability and reproducibility as some objective methods.

In evaluation of a compound of unknown activity, it is important to note that the whole range of qualitative changes produced by a drug and the quantitative relationship between them. It is iknlikely that a drug can be properly evaluated until most of the major tests have been performed under conditions that are similar, in a single animal spicies and by the same route of ^MI administration. More often than not one may tend to confuse matters by extending the range of variables - By mixing up as many different animal species, preparations, conditions and routes of administration as possible in investigating the different actions of a drug. In this way an enormous data is accumulated which is almost impossible to integrate. The value of obtaining multiple data from the sane species, preferably from the same animal, cannot be overemphasised. And from such data the dose-response relations for v different drug actions can be more meani fully compared and then be extrapolated to their appearance in man.

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*

EXPERIMENTAL

THE EFFECT ON BLOOD PRESSURE OF CMP II T OF RAT

METHOD

The rat was weighed 20gm and injected with urathane, after calcutating the dose depending on the weight (0.6% mis per gm). The rats were then left for sometime until they have complete anaesthesia. When anesthetised, the rats were connulated, before connulation of blood vessels, a connula S/' was put in the trachea to facilitate breathing. Then the coronary artery was connulated, followed by a vein in the hind legs i.e. The connula to the artery was connected through transmitter tubing to the recording machine, and also connected to a syringe containing heparmised normal saline. Where as the one at the vein is the one through which the drugs were injected, but crnnular v/as always connected to a syringe containing htpannised normal saline. The heparin prevents formation of clots. After connuation the animal blodd pressure was left to normalise for about 15 - 20 minutes after which a mean blood pressure reading was taken.

Then the animal was injected with the drug 0.?mg start. Then blood pressure bfith systolic and diastolic taken after every 5 minutes for about one hour. Also in another rat the cummulative effect of the drug was observed by injecting a first dose of 0.2 mg then take reading s after which another dose of ,0.4 mg was injected and again the blood pressure readings taken.

A blank experiment was also carried out where a rat was connulated and attached to machine recorder, No injection of vehicle or normal saline of any drug but blood pressure readings were taken until the animal died.

EFFECT OF CUP IIT ON SMOOTH MUSCLE OF GUINEA PIG ILEUM

AND ALSO COMPARING WITH OTHER DRUG HAVING CONTRACTILE EFFECT

METHOD

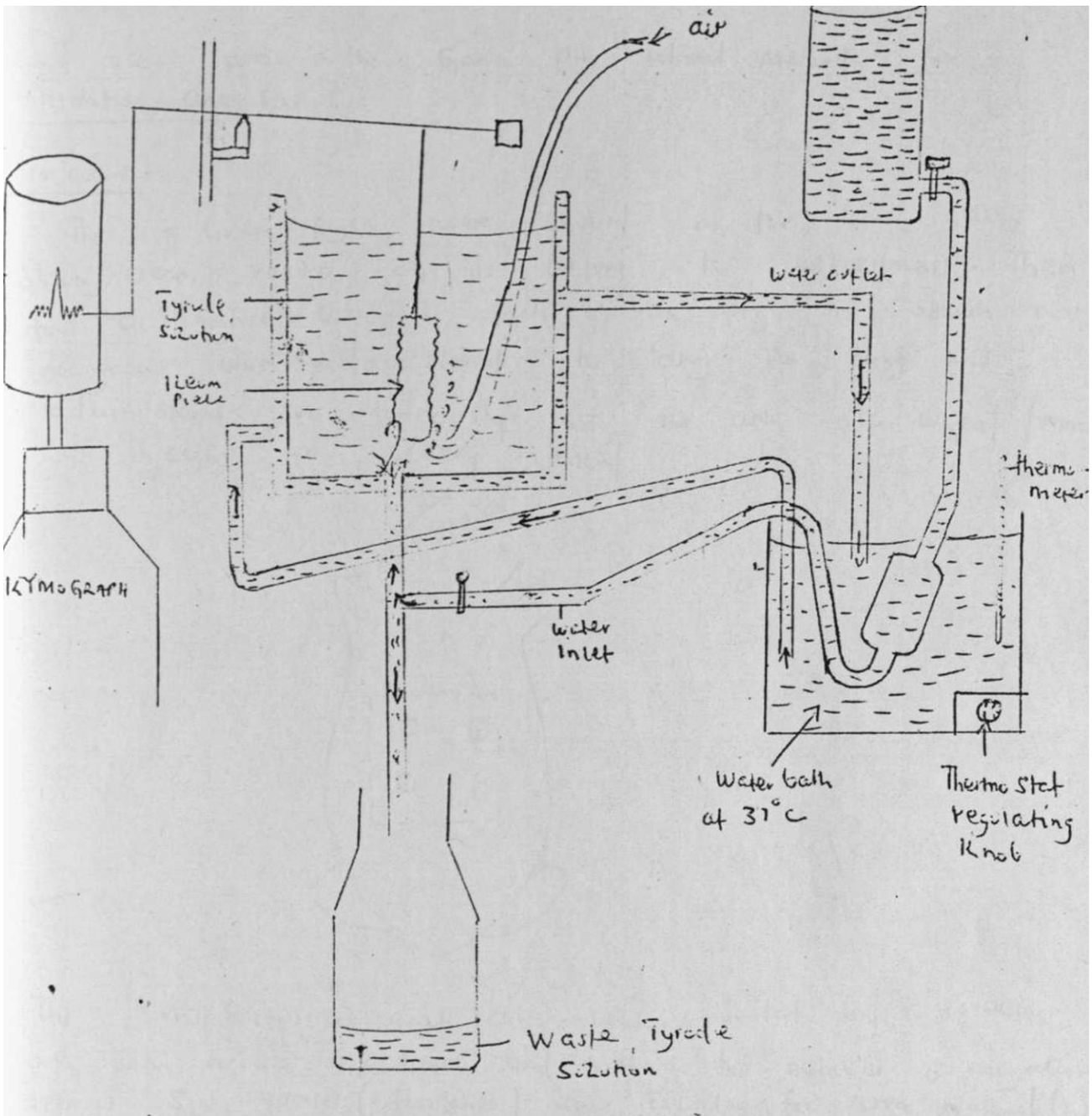
PREPARATION OF TYRODES SOLUTION^ LITRES)

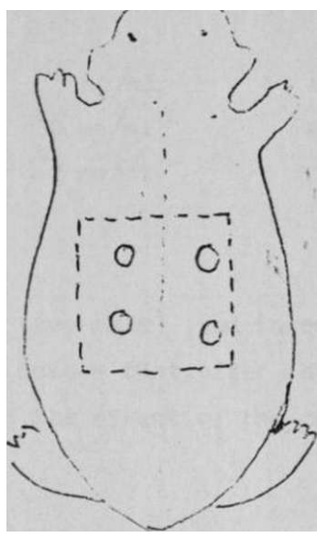
The following substances were weighed and dissolved in distilled water at thesame time, except the calcium chloride which was dissolved last.

Substance	Weight gm
Sodium Chloride	40
Potassium Chloride	1
Calcium Chloride	1
lagnesium Chloride	0.5
Sodium dihydrogen Phosphate	0.25
Sodium Hydrogen Carbonate	5
jlucose	5

DRUGS USED

Acetyl Chlorine (Crystals)	0.2 ug	4 ug
CMP II T	1 mg	2 mg
Histanine (Salt)	2 ug	


air
Tyrode Solution
Ileum Piece
Water outlet
Thermo meter
KYMOGRAPH
Water Inlet
Water bath at 37°C
Thermo Stat regulating Knob
Waste Tyrode Solution



PROPERTIES OF CMP II T ON CENTRAL STIMULANTS

The central stimulant effect of Bemegride (Megimide) and nikethamide were first carried out. Then Bemegride was administered together with CMP II T, same applied to Nikethamide.

DRUGS

			Dose
Bemegride	5 mg/ml	approx. 30Mg/lCg	0.75
Nikethamide	30 mg/ml	approx. lOOmg/lCg	
CMP II T	2 *mg/ml*		

The mice were weighed (two male) and injected intrapentonially the above drugs as shown in the dosage that after calculation. Each mice was injected at a time and the effect of the compounds on the drug observed.

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THE ACTION **OF** CMP II T ON THE ISOLATED MAMMALIAN HEART

LANGENDORFF PREPARATION

PURPOSE OF EXPERIMENT

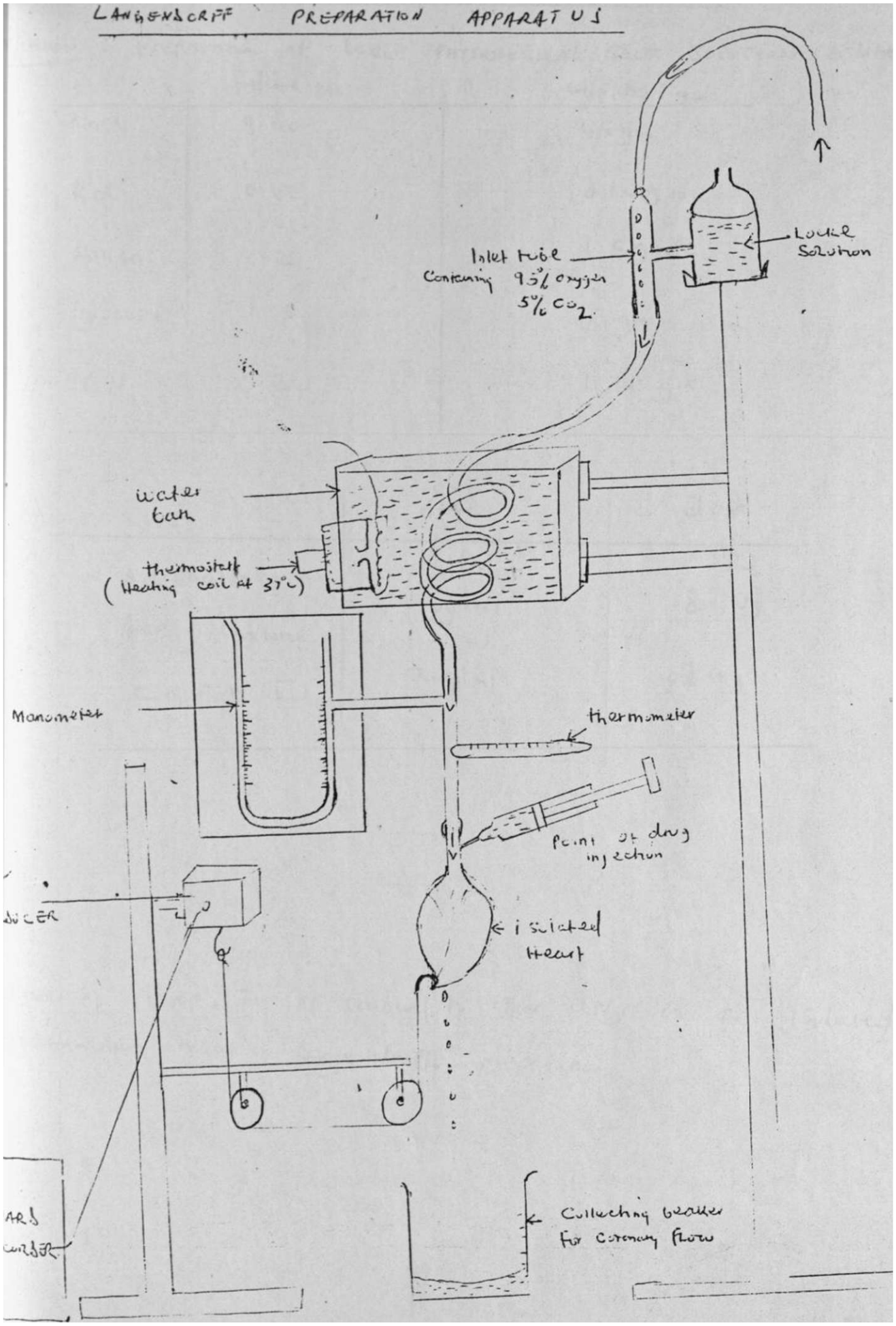
To investigate the drug action on cardiac muscle (without the modifying influence of blood pressure control system) and on the coronary circulation.

METHOD

A rabbit was killed by a blow on the head and chest wall and rib cage quickly opened. This preparation was carried with speed but also with care to ensure that the heart is not damaged. The whole heart was removed ensuring that at least one cm of the aorta is left intact. The aorta is quite easily recognised as the thick walled, white vessel emerging from the left side of the heart.

Immediately the heart was isolated frcm the animal. It was placed into a dish of warm oxygenated Locke solution, and squeezed gently to wash out blood which would otherwise clot inside the heart. The ear was then freed from extraneous tissue and immediately attached through aorta unto the cannula at the base of the Langendorff apparatus. Air bubbles were enjured free from being tapped in the heart by keeping the perfusion fluid flowing v/hile cannulating. The perfusion fluid enters the aorta (this reverses natural flow since in the intact animal blood leaves the heart via the aorta) and thus forces the aortic value to close (again reversing natural order). This effectively prevents flow through the heart chambers and the fluid passes intead wholly into the coronary circulation. From the coronary arteries via the coronary veins the perfusion fluid passes into right auricles and escapes the. heart by way of inferior Vena Cave.

The rate of perfusion and oxygenation were adjusted until the heart was beating satisfactorily. At this stage, the heart apex (ventricle or auricles) was hooked attached by a thread through a pulley system to a starling heart Lever. A normal heart beat was recorded over a 2 min. period on the machine recorder (Havard recorder) prior to administration of any drug. Administration of drug was through injecting into the rubber cup just above the cannula


LANGENDORFF PREPARATION APPARATUS
Inlet tube
Containing 95% oxygen
5% CO_2.
Locke Solution
water bath
thermostat
(Heating coil at 37°C)
Manometer
thermometer
Point of drug injection
isolated Heart
Collecting beaker for Coronary flow

laKrteU . pref^-ccl^ *U FtfYS,eL&iCAL. S , u r S ^ L . T l ^ S LbH*

uM *^ i f s l i b c y «*

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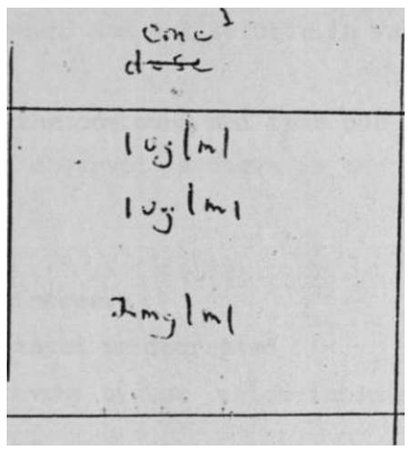

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GENERAL **OBSERVATION OF MICE AFTER INTRAPERITONEAL**

INJECTION WITH CMP II T

METHOD

Several mice were injected with calculated doses of the compound with code CMP IIT. This injection was done intraperitonially. The dose was 1 *mg/kg.* Since the compound was not soluble in water, a very fine suspension of
This was done by tritrating the compound and then put in water and stirred. Various activities were then observed as shown in the plan for evaluating drug action.

I

Pupila size decrease or increase

2. Effect on breathing increased or decreased ,
3. Effect on the central nervous system which include
   a) Sedation/Hypnosis
   b) Stimulation, excitation, convulsions
4. Loss of Righting reflex
5. Anal gesia
6. General anaesthesia

Ssfeacation

Urination

(^ 9. Straff phenomenon.

| 10. Muscle relaxation

11. Restlessness

12. Irritation

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Control

in min	5	10	15	20	25	30	35	40	45	50	55	60
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dation	–	–	–	–								
ypnosis	–	–	–	–								
ghting reflex	–	–	–	–								
nalgesia	–	–	–	–								
General nesthesia	–	–	–	–								
efecation	–	–	–	–								
Urination	–	–	–	–								
Straub	–	–	–	–								
Muscle relaxation	–	–	–	–								
Restlessness	+	–	–	–								
drowsy		–	–	–								
Irritation	–	–	++	–	++							

Wt of mouse 18.5 m.

dose 1 mg/kg

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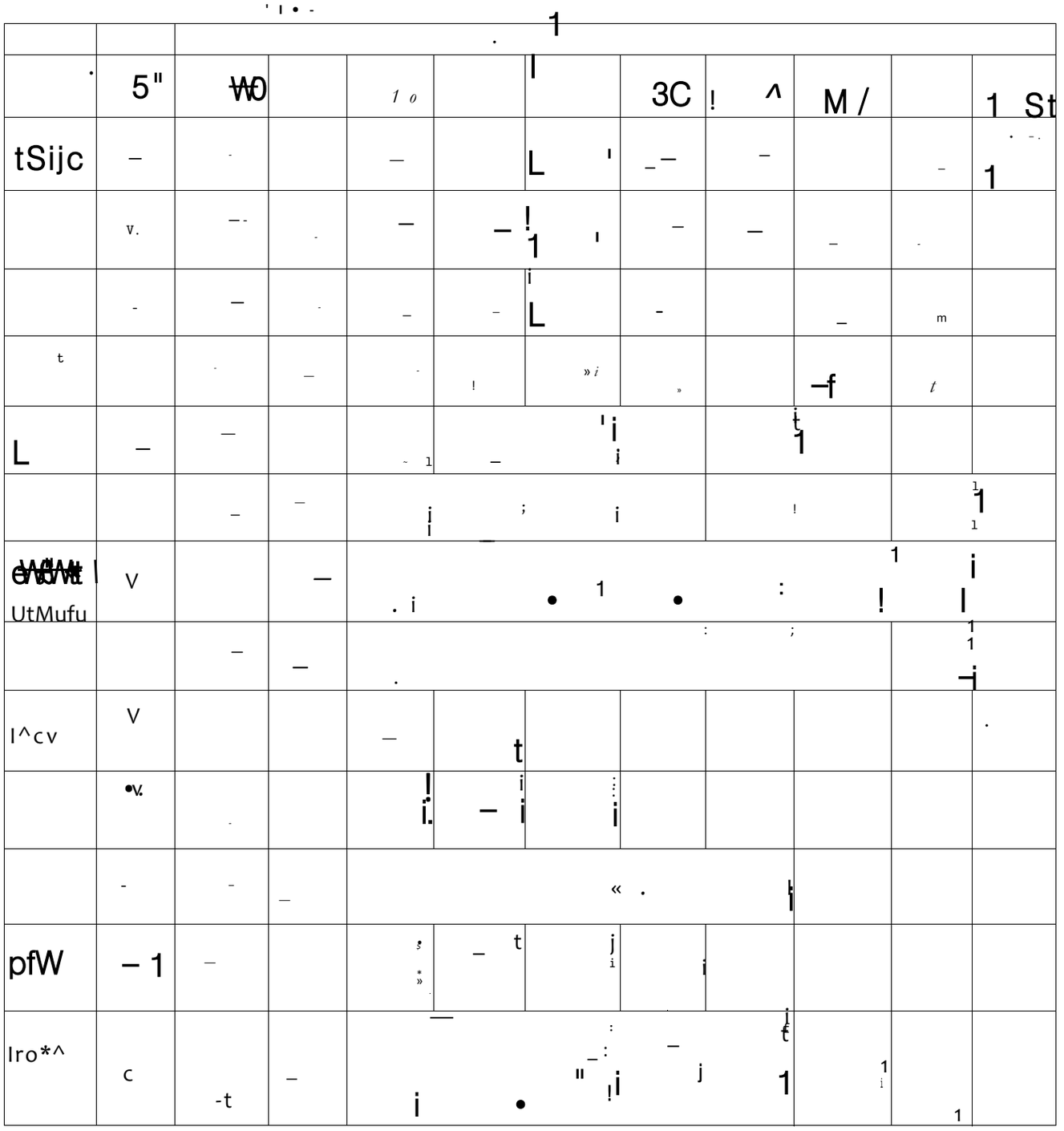

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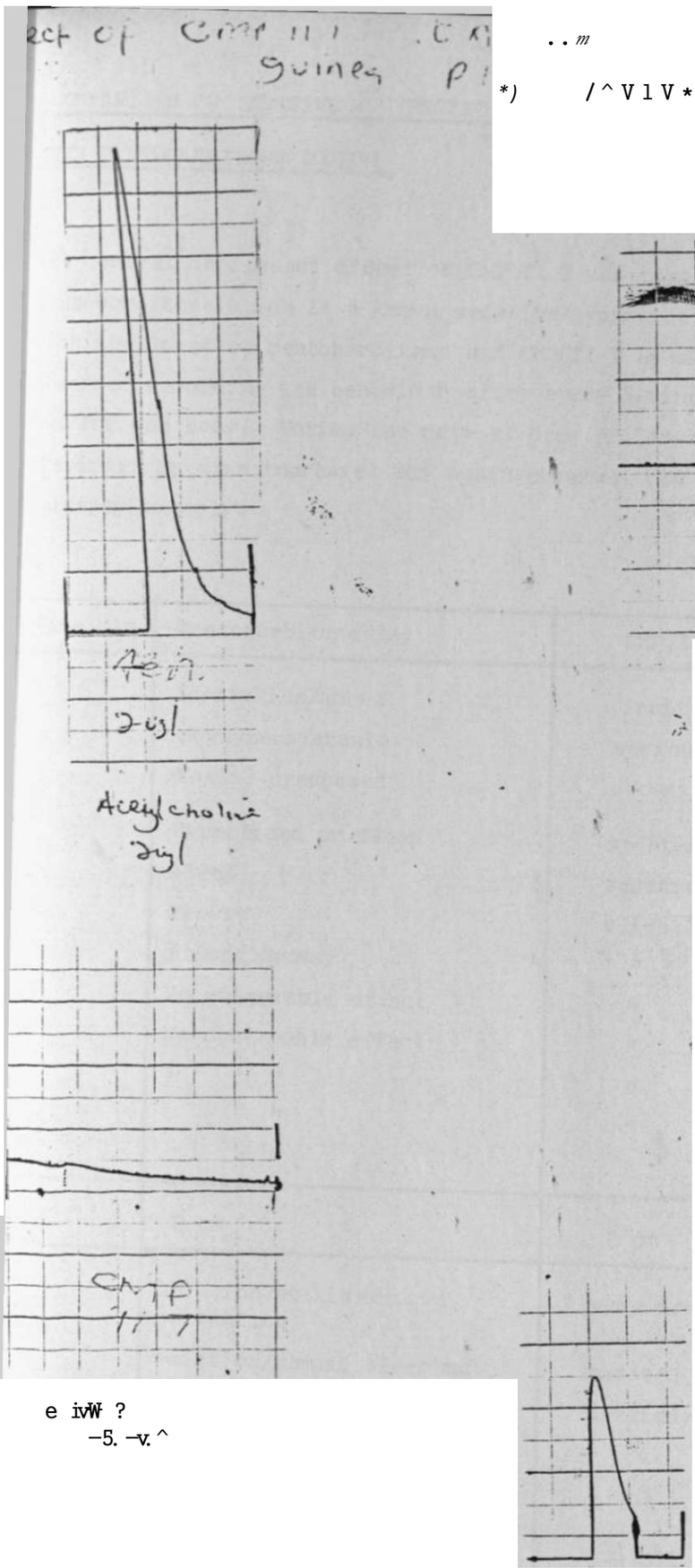
Acetylcholine
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COMPARISON OF SEDATIVE – HYPNOTIC ACTIVITY OF CMP II T

WITH PENTOBARBITONE .SODIUM

.The central deprassant effect of CMP II T was compared with that of a pentobarbitone which is a known sedative–hypnotic. The mice were injected with the doses of pentobarbital and CMP II T as shown in data. Then observed recording the behaviour after every 5 minutes. This was carried out for one hour, Noting the rate of drug action and duration of action. The dose was also increased and again observed thfe animal injected intraperitunuoly.

< ? •

Time Min	Pentobarbitone Img	CMP II T 1 mg
5	Irritation/normal	Irritation
10	drowsyness/ataxia	serious irritation/slight drowsiness
15	ataxia, dreppesed	drowsiness
20	Hypnotised or sleep	sedation/ataxia
25	sleep	sedation
30	drowsy	slightly sedated
35	Slight drowsy	
40	No observable effect	
45	No observable effect	
50	tt	
55	n	
60	•i	t
	2 gm	2 gm
5	Sedation/ataxia/nuscle relaxation	very irritated at site of injection
10	sedation/almost sleeping	sedated slightly
15	sleeps	sedated/ataxia/slowed breathing
20	sleeps	
25	sedated/ataxia	
30	slightly sedated	
35	t	
40	No observable effect	
45	tt	slight sedation S
50	tt	
55	>l M	
L		tt tt

SQMPARISON OF SEDATIVE - HYPNOTIC ACTIVITY OF CMP II T WITH

gDIUM PENTOBARBITONE

'ime lin	Pentobarbitone (1 mg)	CMP II T (1 mg)
•	Irritation/normal	Irritation
to	drowsy/ataxia	drowsy/irritation
k	drowsy/ataxia	drowsy/sedated
D	sedated	sedation
5	drowsy	sedation
D	slightly drowsy	slightly sedated/irritation
5	no observable effect	
h 3		No observable effect
D		
i		n
1		

me n	Pentobarbitone 2 mg	CMP II T (1 mg)
	drowsy/ataxia	Irritation/slightly drowsy
	drowsy/ataxia	sedated/ataxia
	sedated/ataxia	sedated
	Hypnosis	sedated
	Hypnosis	drowsy/sedation
	Hypnosis	
	Hypnosis	severe irritation
	drowsy/sedated	no observable effect
	drowsy	
	Slightly drowsy	

e 50 gm/kg body vt of Pentobarbitone
CMP II T

ACTION OF CUP II T ON STANDARD BACTERIAL CELLS

Cone in ug.	Staphilocucus aureus	Pseudomonal aeroginosa	Klebsiella	Eschelichia Coli
10	-	-	–	-
50	-	-	-	-
100	-	-	-	-
500	-		-	-
1000	-	-	-	-

This compound does not seem to have any antibacterial activity at the above concentration using the standard organisms.

A S* efs Mf<vT (TP LccvH. ^eXTlteTlc , r Oi

c^mP ll T^ /Nrw S C^mP/VI'li (0 C, WITH KNviftl Coc/H– WAilsnhzTiQ-

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• O–IIML

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V 'SstifChU Qcxyr in

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ANTICONVULSANT ACTIVITY TESTING OF CMP IIT

Drugs – CMP II T 2 gm/ml Dose 30 mg/Kg
Bemegride 5 mg/ml 30 mg/Kg
Nikethamide 30 mg/m 100 *mg/kg*
S

Results	OBSERVATIONS		
	3 min	5 min	7 min
Bemegride Vt of mice 24.9 g rose 30 mg/^Cg rose given 0.75 mg in 1.14	Convulsions	Convulsions	animal died
Bemegride + CMP IIT 0.75 mg 1 mg	2 mih Convulsion + muscle rigidity	10 min slight convulsion 20 minutes and was just depressed	Animal never died
Control – Bemegride + *ater D.75 mg 5 mis	3 min Convulsions	5 min Convulsions	7 min 5 sec animal died
Nikethamide •ft of mice 25mg lose 30 mg/ml	1 min Convulsions	3 min Convulsive state	10 min Convulsion animal never died
Nikethamide + CMP IIT 10 mg/nl 1 mg »t of mice 25 mg.	1 min Irritation	2 min Convulsions and animal very excited straub phenomenon	4 min slight convulsion and animal never died
Nikethamide + water 10 mg/ml 0.5 mis LOO *mg/kg* k of 24.8 mg(Mice)	2 min Convulsions	5 min Convulsive state	animal still a bit convulsive at 10 min but never died after 60 min

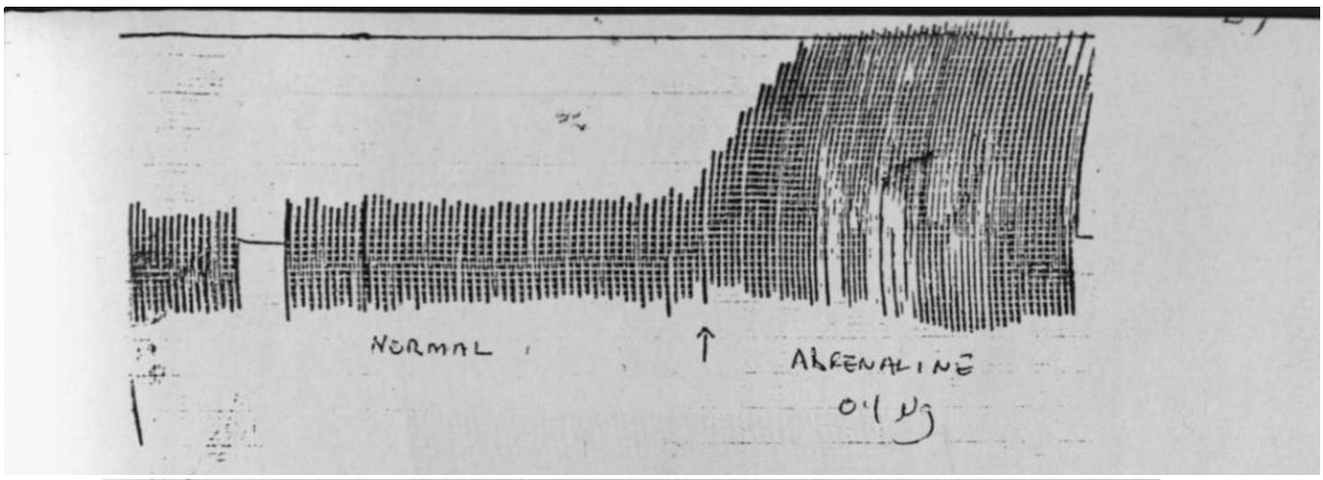
U

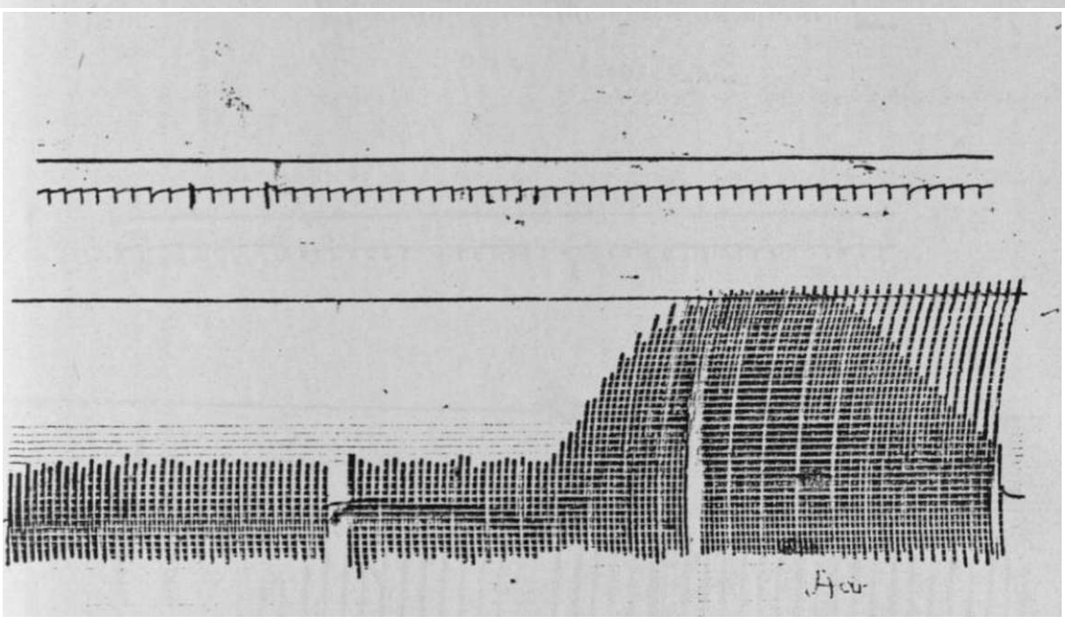
NTICONVULSANT ACTIVITY TEST OF CUP II T

rugs: same as for first mice also some dose

ESULTS

RUGS		OBSERVATIONS	
onegride t of mice 25 g ose 30 mg/fcg	3R min Convulsions	5 min Convulsions	6 min animal died
emegride + CUP IIT cse 0.75 mg l mg	3 min animal looks excited + muscle rigidity slightly	10 min animal hAs slight conv–ulsions 20 mins later the animal just looked depressed	60 min later Animal never died
emegride + water •75mg 0.5 mis	3 min animl is excited with slight conv–ulsions	5 min convulsions	6 min 30 sec animal died
.k^thamide : of mice 25 g >se 70 mg/ml	1 min convulsive and excited	5 min convulsive	animal remained in convulsive state but not severe.and never died
kethamide 4 IP II T 1 mg/ml l mg of mice 24 g	2 min Irritation very excited strab phenomenon	4 min slight convul–sions	animal recovered from convulsive state after 40 minutes.
kethamide + Water mg/ml 0.5 mis	min animal very excited and signs of convulsions	5 min Convulsive fate	animal died after 10 minutes





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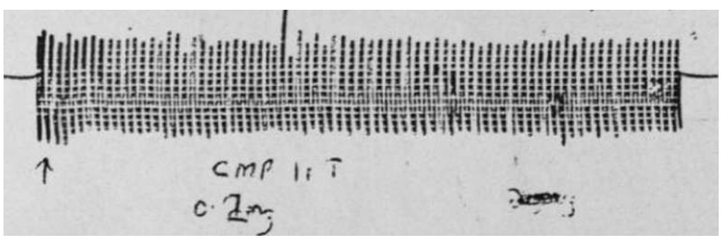

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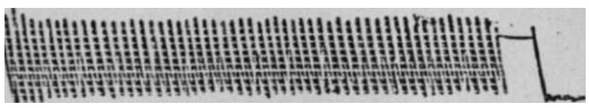

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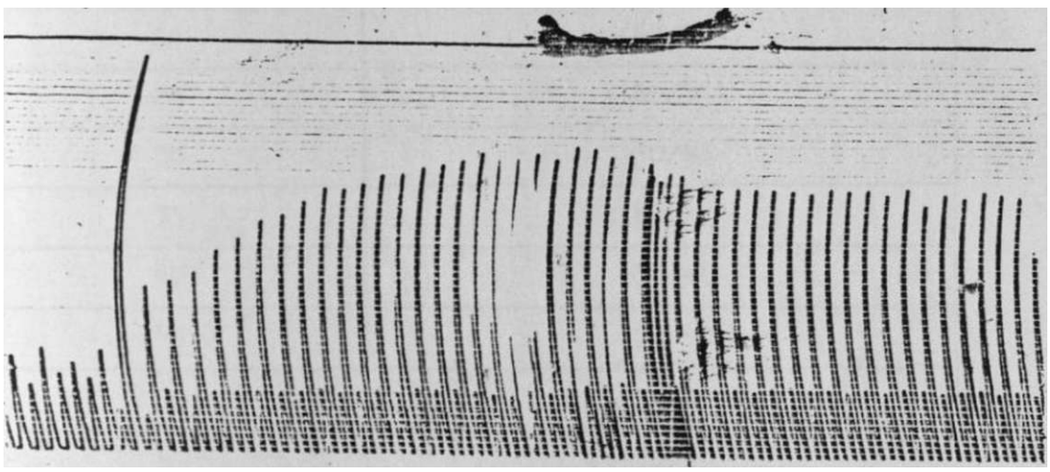

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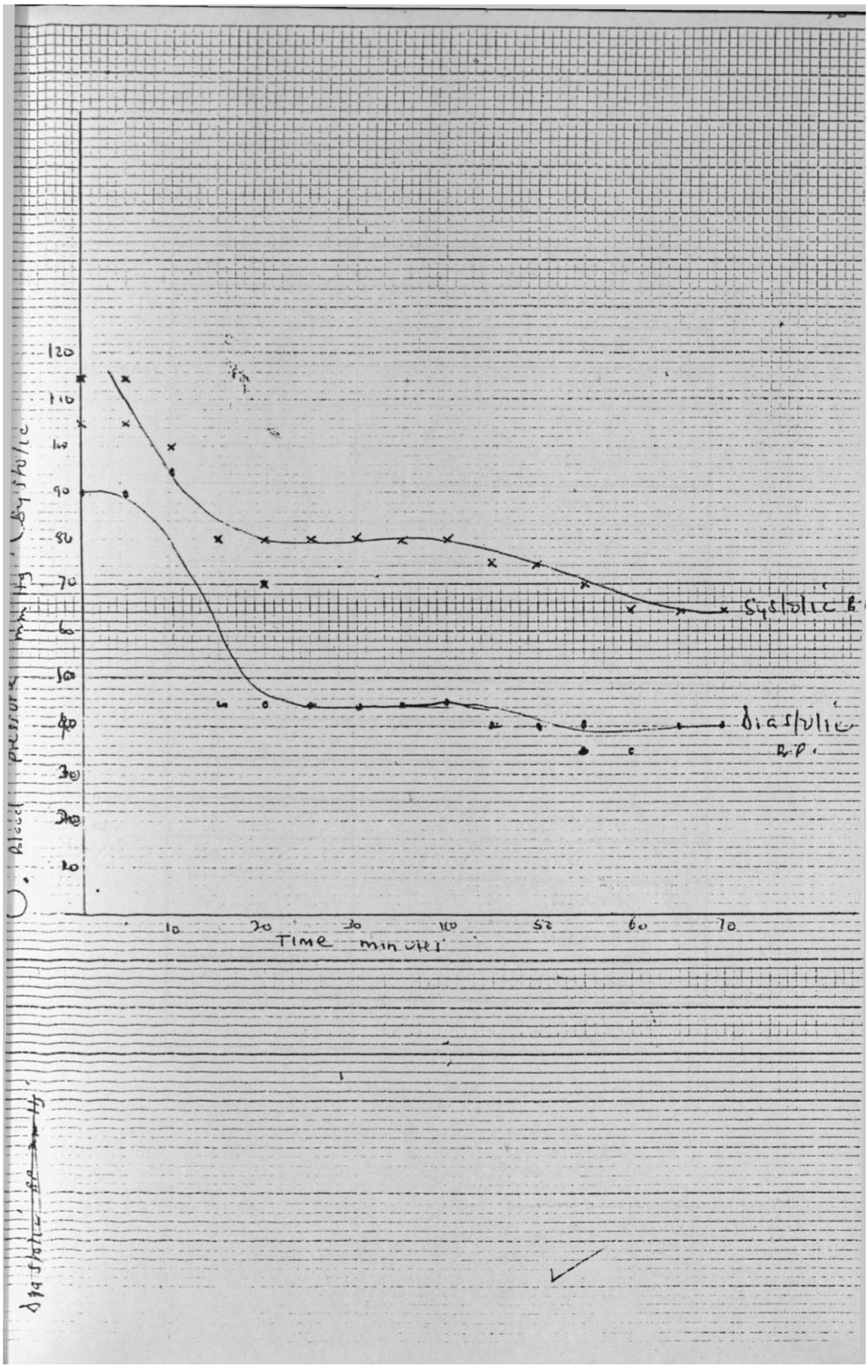
RESULTS!

Weight of rat 250.6 g.

Volume of urathane injected 1.5 mis.

1. Mean blood pressure 105 mm Hg.

TIME Min	Blood pressure mm Hg.
0	10^/90 j .— ' .
5	105/90
10	100/95
15	e.o/us
20	'80 A 5
25	80/h 5
30	8o/t»5
55	80/1+5
) 'to	80 A 5
^	. 75AO
50	75/'»0
55	70/'»0
6o	65/35
65	65/tfO
70	b5/U0


Blood pressure mm Hg
120
110
100
90
80
70
60
50
40
30
20
10
20
30
40
50
60
70
Time minutes
Systolic B.P.
Diastolic B.P.

2. Y/t. of rat 18<4.5 g.

Dose of urathane given 1.5 ml.

Mean Blood Pressure 155 mm Jig.

	Time Kin	B.T. mm Hg.
1st dose 0.2 mg.	0	180/1*»0
	5	y 155/110
	10	150/105
	15	1" 5/95
	20	i'»o/9o
	25	lho/9o
(	30	l^o/9o
	35	1^o/9o
		i«fo/8o
		Ho/8o
?nd dose mg.	0	1*40/80
	5	ll+o/9o
	10	11+0/95
	15 W	135/95
	20	130/95
	25	125/100
	30	110/100
	ho	l ' 105/100
	^5	Anima] died at 60 mm Hg

BLAnr CANNULATION

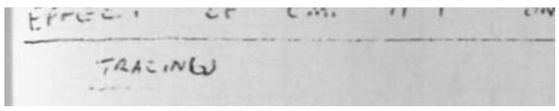
Weight of mice 162 gm

Dose of Urathane 1 ml

Mean blood pressure 120 mm Hg

rime Min	B.P mm Hg
0	120/110
5	120/110
10	125/110
15	125/115
20	125/115
?5	125/115
30	120/110
35	120/110
40	120/110
50	120/110
60	120/110
70	120/110
80	120/110
90	120/110

The animal died after 50 minutes



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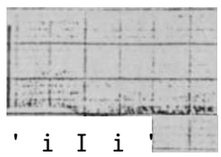

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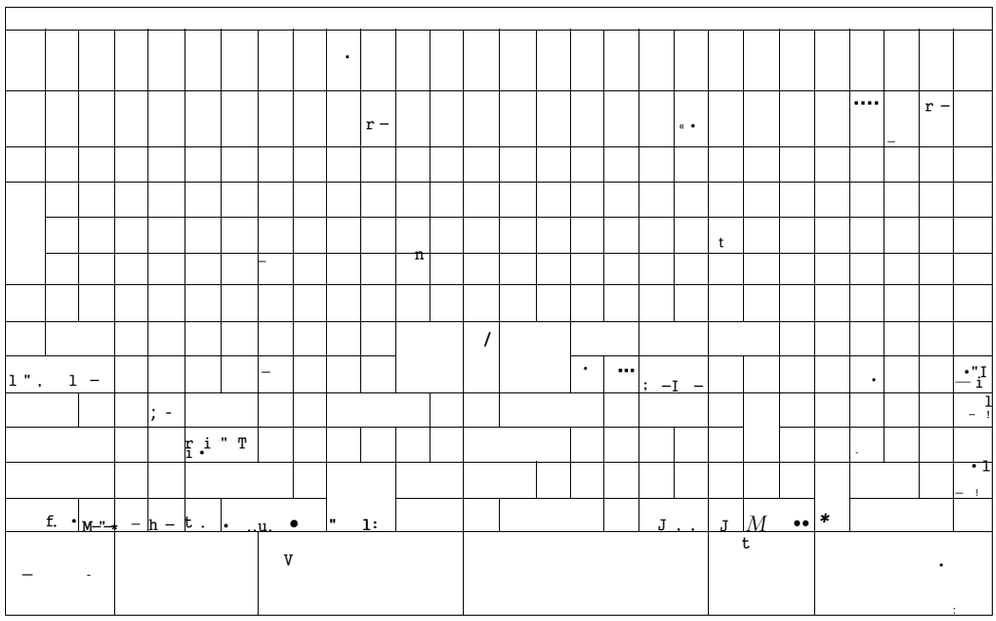

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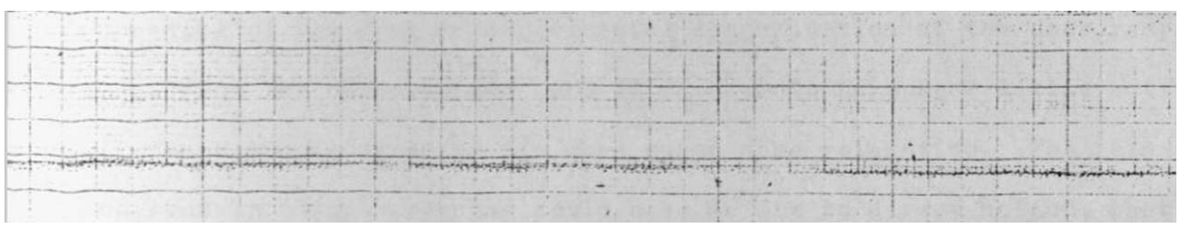

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The discussion will mainly deal with the Thormacological properties of the drug after screening and also some det/yiled study of some properties thought to be of value in drug development.

There were several activities of drug observed in the injection (1/F) of CMP II T in mice. The following activities were observed:-

Decrease in pupil size

Slowed breathing

Sedation/Hypnosis

Oefcocation

Musclc relaxation

Restlessness

Irritation

Loss of tighting reflex.

Out of the above activities irritation was very prominent in all the mice used, this is common with products of croton species. Then the following activities from the above observation wore studied in detail.

P^ffect on the guinea pig smooth muscle of the ileum. The guinea 3pig elium lacks intrinsic activity and therefore any response observed is due to the drug injected in the medium. As such the ileum is used in screening of new drug or experimental determination of the dose response cure. From the observations, CMR II T seems to have sgme little activity tfn smooth musclc directly, it does cause same relaxation. The relaxation observed in blind screening could have be''due to direct action, that it could have been acting centrally like other central muscle relaxants e.g. Benzodiazepines (Diazepam). This compound also seems to antagonise the effect of acetycholine cv V«' in smooth muscle, it also antagonises histamine. This antagonism could be direct or indirect i.e. the compound could be having affinity for the receptors biit no intrinsic activity or could be inducing production of physiological antagonists of both acetylcholine and histamine.

Thc sedative activity of CMP II T as compared to that due to Pentobabi tone. A variety of drugs can produce a state of depression of the central narvous system resembling normal sleep. Such drugs are referred as sedative hypnotics. In smaller doses many of these drugs can produce a state of dowsiness and when used in this manner, referred to as sedatives. When used in larger doses, hypnotics may produce anaesthesia, poisoning and death. These progressive dose - related effects may bo indicated as followss-

Sedation Hypnosis Anaesthesia Coma Death

Barbiturates are important central nervous system deppressants. They can cause all the above effects depending on the dose comparing the effect of Pentobarbitone with that of CMP II T on the central nervous system, it is observed that barbitrates cause a more pronouned and faster CNS deppression. Where as CMP II T has a delayed onset of action but a prolonged action as compared to the short acting barbiturate. To improve the CNS effects of CMr II T, structural changes in this compound could be done.

Local anesthetics are drugs employed to produce & transient and reversible loss of sensation in a circumscribed area of the body. They achieve this effect bv interferring with nerve conduction. Electrophysiologic studies indicate that the local anesthetics do not alter the resting membrane potential or threshold potential of nerves. They act on th« rate of rise of the depolarization phase of the action potential. Since depolarisation does not reach the point of which firing occurs, propagated action potential fails to occur.

On comparing the local anesthetic activity of the unknown drug with that of standard lbcal anaesthetics I.ignocaine, procaire and a control using normal-saline. It is observed that the new compound has lower local anaesthetic activity. Although CMP II T has some local anaesthetic activity, it nay be improved by carrying out structural modification.

A variety of drugs lower the reflex excitability of the central nervous system, stimulate respiration, cause hyperre flexia and induce conuulsions in a dose - dependent fashion. Because of their awakening cffect they are often referred to as analeptics. These drugs are mostly of toxicologic interest, although they may occassionally be used as respiratory stimulnnts strychmine picrotoxin, nikethamide, bemegride, mothylxanthines such as caffnrie belong to this group .

When mice nre injected win (I.P) c-ny an in the experiment 0.75 mg of bemegride, this induced conuulsions which resulted into the death of mic£. But when injected bemrrride followed by CMP II T (unknown drug). The conuulsions were rcduced and animal never died. This shows this v/ compound has anticonvulsant activity. A control experiment was done by injecting water since the formulation was a suspension of CMP II T in water. Also mice were treated as above with nikethamide which is also a CNS stimulant and the effect observed is that the unknown drug has anticonvulsant activity since it counteracts both bemegride and nikethamide induced conuulsions.

Cardivascular system effects de^lt with in this project are mainly the effect on smooth muscle of mammalian heart i.e Rabbit and blood pressure of.a rats monitored through canulation and transmission to machine detector and recorder. From the experimental results it is observed that the unknown drug CMP II T'has no direct effect on the myocardium. This compound nlso when injected together with adrenaline which increases rate of contraction of the smooth muscle of myocardia has no effect i.e. antagonism. Mso acehylcholine was injected, and the expectcd effect was observed, i.e. lowering in heart rate Acetylcho- line acts on the sino artrial node which is also termed as the pase maker, here it acts as the transmitter substnnce hence lowering the heart rate.

On the blood pressure of the rat, CMP II T is observed to lower the blood pressure of the rat. From the results this compound lowers both the systolic and diastolic pressures of the heart. The magnitude i.e. the difference b«>twf»en th" blood pressure is very high as compared to

that of the control, where the animal was just connulated and the blood pressure monitored. Also these compound CHF II T seems to have a sustained action on the blood pressure, i.e. there is a constant and maintained low blood pressure in all the mice treated with this CFD for about *kO* minutes.'

The efficacy and specificity of hypotensive drugs in treatment of patients with high blood pressure have been challenged by many investigators who have shown that p.laccbos, reassarance, etc can produce the same results as medical therapy. The reasons why so many drugs are alleged to be effective include failure to control the clinical observations by the use of placebos, failure to recognise the extreme lability of the blood pressure in many patients and failure to distinguish between relief of symptoms and hypotensive effects. However sooner or later in the course of his disease, nearly every hypertensive patient, is placed on a trial period of therapy with vesodepressor drugs. Treatment is perhaps especially indicated if the patient is seen very early and has a rather labile blood pressure, if a cerebrovascular accident or hypertensive encephalopathy episode is imminent, or if marked symptomatic rclieT is experienced. Any vasodilating drug which fulfils the criteria demanded in the treatment of arterial hypertension should have a constant, sustained action, should act by dilating the arterioles over all the constricted areas, should not give rise to unpleasant symptoms or side effects and should maintain the normal function of the organs partidularly the heart and kidneys.

Since it has been observed that CMF II T has no direct effect on mycordium, then it must be acting by oth^r mechanism in lowering the blood pressure, this is likely to be by causing vasodilation of arterioles.

COHCIOSICW:

A whole range of activities or qualitative changes produced by the substance CMP II T and also quantitative relationship between them have been evaluated. This is usally so in screening of unknown drug. From the general observations, specific activities were investigated further. These activities are exhaustedly discussed in the discussion. From thpse specific activities it can be noted that this compound has profound effect in the cardiovascular system mainly hypotension. Although for a compound to be of therapeutic valve in hypertension, it must have a constant sustained lowering of blood pressure. From the results this compound (CJ-lP II T) does not seem to have a prolonged duration of action i.e the constant sustained lowering of blood pressure. Although have been using rats to demonstrate the hypotensive action of this compound, it docs not always follow that the effects observed in animals will be the same and also qualitatively and quantitatively in man as in laboratory animals.

Also this compound seems to have some profound effects on the central nervous system. The sedative effect of this compound has been compared to that of known central nervous system depressants i.e. barbitufa (pentobarbitone). From the depressant action, it was further infesti-gnted the anticonuulsant activity of CMP TI T on bemegride and nikethamide induced eonuulsions. 7/ell although this compound has anticonuulsant activity from the results it dors not appear to fully counteract to convulsion. Hence alot of study mainly in modification of the structure of this compound could J-rad to a new drug which is actually the essence of drug development in prevntiop, control and treatment of diseases.

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