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May 2, 1984

Dear Mr. Lotsoff:

I have enclosed the report on the literature on ibogaine that I contracted to review for the Dora Weiner Foundation. To preserve confidentiality, I have used:

Compound-X or CX for ibogaine	
X2	ibogaline
X3	iboxygaine

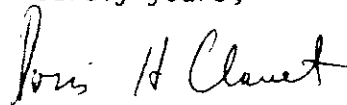
in the report, which was typed by a professional typist with no training in science.

You may be disappointed with my conclusion that there is no important evidence in this literature that suggests that ibogaine would be useful in treating opiate addiction. I am not certain, however, that one would expect, or wish, that ibogaine should act like an opiate. I will discuss some of my thinking about possible mechanisms of action with you.

In spite of my conclusions about supporting literature, I am not adverse to pilot clinical studies for confirmation of your earlier studies, with certain precautions concerning ibogaine toxicity, especially in at-risk groups, clinical setting, double-blind tests, etc., because your 'invention' is a new approach to the treatment of addiction.

I am sending your reprints back as a separate package, or, by hand, should the opportunity arise.

Sincerely yours,



Doris H. Clouet, Ph.D.

## LITERATURE REPORT ON COMPOUND-X

### A. Review of Scientific Literature (as supplied by Mr. Lotsoff)

- (1) Caeruloplasmin, an oxidative enzyme, catalyzes the oxidation of noradrenalin and serotonin to adrenochrome-like catabolites. Several compounds were tested to measure interference of caeruloplasmin activity. LSD, 2-Bromo LSD and Compound-X increased the oxidation of NA and inhibited this oxidation at very high drug concentrations. Harmine and harmol inhibited the oxidations at  $10^{-3}$  and  $10^{-4}$ M concentrations. Many phenothiazines have enhancing effects on the oxidation of NA and 5-HT by caeruloplasmin at very high drug concentrations as does haloperidol. Amitriptyline has an inhibitory effect.

This paper suggests that compound-X can effect the metabolism of NA and 5-HT. Since caeruloplasmin is not considered a normal route of catabolism for biogenic amines, it is not an important reaction. Almost any drug at  $10^{-3}$ M concentration will have an effect on an enzyme reaction, if only by mass action.

- (2) This paper is a repetition of paper 1.
- (3) The pressor actions in hens of substance P were antagonized by various drugs. Substance P produced a biphasic effect. The depressor phase was inhibited by compound-x and many other drugs but the responses were inconsistent and variable.

This paper offers a slight evidence of a relationship between Substance P and Compound-X.

- (4) Convulsant and anti-extensor seizure activity of excitant drugs were measured in mice. Cocaine, methylphenidate, Compound-X and desoxyephedrine all produced circling activity, tremors and hyperlocomotor activity. These compounds also abolish the tonic extensor seizure produced by electroshock or pentylenetetrazol and not by caffeine or strychnine.

This evidence indicates that compound-x resembles other excitants in depressing extensor activity, but differs from anticonvulsants such as dilantin or phenobarbital that antagonize caffeine and strychnine-induced convulsions as well.

- (5) Vinblastin and vincristine were examined for their ability to deplete neurotransmitters. Injected i.p. vinblastin decrease NE levels in heart and salivary gland while vincristine does not alter NE levels in tissues. Evidently vinblastin does not cross the BBB.

Vinblastin which contains one nucleus of Compound-X is able to alter the levels of NE and acetylcholine in heart.

- (6) Tabernanthine, a substance closely related to compound-x, causes myoclonia, convulsions, tremors when abused by man. In brain areas of the rat, catecholamine levels (CA) were not affected by the drug but turnover time was slightly decreased of DA in striatum and NA in hypothalamus. At hypobaric pressures tabernanthine administration was able to reverse partially the decreased turnover of both DA and NA, with a greater effect on DA.

These results suggest a relationship between tabernanthine and brain catecholamines.

- (7) This report describes metamaminol as a false neurotransmitter. This compound does not cross the BBB, but has hypotensive properties in man.

The relevance of this paper is not seen unless it is to introduce the concept of false neurotransmitters.

- (8) The cerebellar system related to locomotion and gait was examined for its responses to compound-X<sup>2</sup> and oxotremorine. Episodes of electrical sustained rhythmic activity followed the administration of harmaline or compound-X<sup>2</sup>. A synchronization of responses in olivary nuclei and Purkinje cells was seen. Harmaline is an MAO inhibitor but Compound-X<sup>2</sup> is not. Oxytremorine produced tremor and convulsions but no rhythmic electrical activity in the olivocerebellar system. Anticholinergics block only Oxytremorine.

These data show that harmaline- or compound X<sup>2</sup>-induced tremor is generated by specific climbing fibers in the cat cerebellum.

- (9) This is a thesis describing the toxicity of Compound-X. It is classed with LSD by the FDA since it is a true hallucinogen. Among its other pharmacological effects are: reversible competitive inhibition of 5-HT transport in platelets, inhibition of intestinal contraction, typical EEG arousal pattern, direct inhibitory and central stimulatory effect on heart, tremor and excitation. The toxic dose in dog, gpi and rabbit is about 500 mg/kg. Most responses occurred after doses of 1-10 mg/kg.

Compound-X may be considered a complex analog of 5-HT. It was compared to 5-HT in these studies. The LD<sub>50</sub> of compound-X in rodents was 145-175 mg/kg i.p. Death from lethal doses occurred 7-10 minutes after the i.p. injection. No deaths were observed after 6 hours. Ethanol potentiated the effect, reducing the LD<sub>50</sub> to 105 mg/kg in the rat. Iproniazid pretreatment also enhanced the toxicity. Atropine blocked the effects of Compound-X and 5-HT of depressing blood pressure. Both drugs caused depressor effects, although 5-HT produced a triphasic effect.

The author concludes that there was one area of similarity between Compound-X and 5-HT: parasympathetic activity and that there was little support for the hypothesis that mental illness results from a disarrangement of 5-HT actions. The toxicity data in rodents is excellent. There was no gross histological damage after chronic administration of Compound-X at 10 mg/kg or 50 mg/kg. Serotonin did produce damage at lower doses.

(10) Compound-X and harmine have psychomimetic effects in man with excitation, inebria and hallucinations. The natives of French West Africa use harmine and compound-x without experiencing hallucinations. Compound-X produces hypotension in man but also potentiates the pressor response to adrenalin.

In sheep, dogs and cats excitants were studied.

	NE	H.R.	Adren.	Ach	Hist.
	B <sub>1</sub> Pr.	biphasic	B <sub>1</sub> Pr. ↑ H.R.	B <sub>1</sub> Pr. ↓ H.R. ↑	B <sub>1</sub> Pr. ↓ H.R. ↑
Dog	↑	biphasic	↑	↓	↓
Sheep	↑	--	↑	↓	↓
Cats	↑	--	↑ el ↑	↓	-

Compound-X increased B<sub>1</sub> Pr and increased H.R. It prevented Ach-induced decrease in B. Pr. It also potentiated pressor responses to 5-HT.

In conscious dogs, Compound-X produced increased anxiety, agitation, nervousness, body tremor, lack of recognition of regular handler. These effects and increased B<sub>1</sub> Prs. were antagonized by amobarbital or librium.

In conscious cats, Compound-X produced dilated pupils, excitation tremors and rage. Atorpine reduced B<sub>1</sub> Pressure increases but not behavioral effects.

Yohimbine, harmine and Compound-X produce an anxiety state resulting from stimulation of central alerting systems.

- (11) A similarity of interatomic distance in a part of the 5-HT, LSD, psilocin, bufotenin and Compound-X molecules has been found. It is suggested that this conformation binds to 5-HT binding sites. All of the drugs produce hallucinations.
- (12) This report describes the effect of hallucinogens or aggressiveness in mice. Compound-X decreased aggressiveness in isolated mice as did the other hallucinogens.
- (13) Many drugs including Compound-X inhibit the uptake of 5-HT by platelets.
- (14) This is a patent application for the use of Compound-X in interrupting the narcotic addiction syndrome. It starts with a description of the early history of Compound-X, its chemistry and pharmacological properties. There is no mention of Compound-X in relationship with addiction, other than a paper by Schneider on potentiation of morphine effect by Compound-X.

The "invention" of Compound-X as a disrupter of heroin addiction is supported by case histories. Five out of seven addicts had their addiction interrupted by Compound-X. A large dose of Compound-X produced effects that lasted for 24-30 hours with phase 1=excitation with auditory and visual hallucinations, phase 2=high energy state, phase 3=sleep. The 5 case histories follow. A dose of 500-600mg compound-x is given orally to a heroin addict after a week a second dose is given followed by increasing doses until 1000mg is reached. There was no hallucinations after last doses.

Patients remained heroin-free for 6-36 months. There are a number of problems with these case histories. No mention is made of physicians presence, laboratory surroundings or double-blind use. The results are anecdotal rather than scientific. The high dose of Compound-X used in these patients produced profound, possibly dangerous effects in the subjects.

Several possible modes of action of Compound-X are described. The claims for the patent are also described.

- (15) Harmaline binding in rat brain mitochondrial-synaptosomal membranes: a specific binding site was found near MAO-A in tissue. MAO inhibitors displace harmaline from its binding site. The additional ring in Compound-X and X<sup>2</sup> resulted in a loss of binding activity and MAO inhibition.
- (16) The hypnotic effect of hexobarbital is potentiated by 5-HT. Compound-X enhanced this effect of 5-HT but decreased the sleeping time of reserpine plus hexobarbital. These results of LSD, BOL and Compound-X enhancing 5-HT effects supports the view that hallucinogens affect 5-HT function.
- (17) Compound-X potentiates analgesia produced by morphine in mice. Compound-X enhanced and prolonged the analgesic effect of morphine 3 mg/kg as measured by the tail flick test. Compound-X itself had no analgesic effect up to 40 mg/kg s.c. Compound-X also increased analgesia produced by codeine, demerol and ketobemidone. Compound-X also increased the lethality of morphine: 75 mg of each being equivalent to 400 mg of each drug alone. Compound-X also enhances morphine analgesia in man.
- (18) A fall in blood pressure was found in anesthetized dog, but a rise was found in conscious dog produced by Compound-X. The rise in blood pressure is part of the alerting response.
- (19) In conscious cats, Compound-X produced excitation, piloerection, tremors, evidence of hallucinations, clonic extension of front legs and mewing. The EEG showed typical arousal pattern. The reticular ascending system was implicated in the seizure activity and alerting pattern of EEG which could be blocked by atropine.
- (20) Structure of Compound-X in this paper differs from that described by Dhakir (#9). In mice the ED<sub>50</sub> for tremors was 127ug/animal intracerebrally.
- (21) An animal model for 5-HT receptor activation in rats was discovered. Hallucinogens were injected into lateral ventricle of conscious rat. LSD, DMT and Compound-X produced syndrome, also increased brain DA levels to 139% by Compound-X. 5-HT levels were unaffected. Giving large dose of 5-HTP plus an MAO inhibitor produced the syndrome.
- (22) This report shows that Compound-X did not antagonize glycolysis in frog muscle.
- (23) The intercalation of Compound-X in a model RNA helical structure mimicking the 5-HT receptor is described. The model has been discredited.
- (24) Morphine antagonized the action of Substance P in gpi as did Compound-X. Both drugs also decreased the activity of Substance A.

- (25) Vinblastin and other indole alkaloids inhibited calmodulin-dependent phosphodiesterase (PDE) activity. Vinblastin activity was competitive with calcium-calmodulin. This inhibition acquires the catharanthine moiety which is present in Compound-X.
- (26) The inhibition of 5-HT binding to calf-caudate homogenate binding sites was studied in this report. Many 5-HT agonists and antagonists displaced 5-HT. LSD, methysergide, bufotonin and psilocin were active in the nanomolar range. Compound-X, however, was inactive.
- (27) Same subject and investigators as #26. A second 5-HT binding site was found in calf caudate that was more specific for LSD. Compound-X had no affinity for either site.
- (28) This report described the biosynthesis of Compound-X by its parent plant. In 3 weeks after  $C^{14}$ -tryptophan was injected into the plants 6.7% of the radioactivity was in Compound-X.
- (29) Tremor-producing activity of indole alkaloids was studied in mice. Tabernanthine, Compound-X<sup>2</sup>, harmaline, harmine, Compound-X, compound-X<sup>3</sup>, harmane, and nor-compound-X were all active in producing tremors in mice. The half-life in brain was about 20-30 minutes for all drugs. Compound-X<sup>3</sup> had a 3 compartment elimination curve.
- (30) The inhibition of the cardiac effects of norepinephrine NE on g.p. atria was examined in this report. NE increased beats/min from 135 to 197. Compound-X and 3 related substances all had antagonistic effects on NE stimulation. These compounds, therefore, have a depressor effect directly on heart, although in the whole animal, their effect is hypertensive.
- (31) A number of text books that contained a history of heroin addiction and its various treatments were consulted to see if a hallucinogen has ever been suggested as a therapeutic agent for heroin addiction. No such reference was found.

## B. Classification of Reports

### 1. Not pertinent or obsolete

1, 2, 7, 11, 22, 23, 25, 28

### 2. Substance P Interactions

3 - Pressor effects of P antagonized by C-X.

24- Morphine and CX antagonized action of Substance P in gpi.

### 3. Morphine Interactions

14- CX is interruptor of heroin addiction

17- CX potentiates morphine analgesia in mice and men.

### 4. Excitant Activity in Animals

4- C-X produces convulsions and circling behavior in mice

C-X antagonizes electroshock in pentylenetetrazol extensor activity, but not that of caffeine or strychnine.

- 5- DA turnover in caudate of rat decreased by tabernanthine.
- 10- C-X in dogs produced anxiety, excitation, body tremors and bl. pr. antagonized by librium or amobarbital
- C-X in cats produced tremors, rage, Bl Pr increase antagonized by atropine.

#### 5. Excitant Activity in Man

- 5. Tabernanthine produces convulsions, etc when abused by man
- 10. C-X produces excitation, inebria and hallucinations in man
- C-X abused by West Africans

#### 6. Locomotor Activity in Animals

- 8. C-X<sup>2</sup> produces a rhythmic synchronized electrical response in cerebellum and olivary N of the cat.

#### 7. Toxicity in Animals

- 9. In dog, rabbit, GP LD<sub>100</sub>=500 mg/kg
- In rats LD<sub>50</sub>=145-175 mg/kg ip
- No gross histological damage after chronic 10 or 50 mg/kg
- 22- ED<sub>50</sub> for tremors in mice - 127 ug/mouse intracerebely

#### 8. Blood Pressure Effects

- 3- Pressor effects of Substance P antagonized by C-X
- 9- C-X produces depressor effects on BL Pr.
- 10- C-X produces hypotension in man
- C-X potentiates NE hypertensive effects in man
- 10- C-X BL PR increase antagonized by atropin in cats and dogs
- 18- In conscious dogs and cats CX increases BL PR

#### 9. Other Pharmacological Effects

- 13- CX and other hallucinogens decrease aggressiveness in isolated mice.
- 13- CX inhibits 5-HT uptake by platelets
- 14- CX is interruptor of heroin addiction in mice.
- 15- CX and related cpds do not inhibit MAO
- 16- CX enhances 5-HT potentiation of hexobarbital hypnosis.
- 17- CX enhances morphine analgesia in man
- 26- CX has no affinity for 5-HT binding sites.

#### 10. Excitant Actions in Animals

- 19- EEG after CX showed typical arousal pattern. The reticular ascending system was implicated in the seizure activity and "alerting" pattern of EEG which could be antagonized by atropine.
- 21- In rat model of excitation, LSD, DMT and CX produced syndrome. A large dose of 5-HTP plus an MAO inhibitor also produced syndrome.
- 29- In mice tremors produced by various indole alkaloids with closely related brain levels and half-life of drug in brain of about 20-50 min.

### C. Summary of Literature

Agreement exists in this literature that Compound-X is a hallucinogen as are related compounds that I have designated X<sup>1</sup> and X<sup>2</sup>. When administered to animals CX produces increased blood pressure and a rhythmic synchronized electrical response in the cerebellar-olivary system. Both are signs of the 'alerting' response. At high doses CX produces tremors, inebria, convulsions and hallucinations. CX produces similar effects in man.

There are contradictions concerning the blood pressure responses to CX, apparently related to whether the tests are done on isolated tissue or intact animals and whether the animal is conscious or anesthetized. In conscious animals CX raises blood pressure, an effect antagonized by atropine. CX also potentiates the pressor responses to nor-adrenalin. In man CX potentiates the pressor responses to adrenalin.

There are toxicity studies in animals. The LD<sub>100</sub> seems to be 500 mg/kg. In rats, the LD<sub>50</sub> is 145-175 mg/kg i.p. Tremors were produced in mice after 127ug/mouse was administered intracerebrally. There are no toxicity figures for man.

These are a few reports relating opioid drugs and CX. Both morphine and CX antagonized the stimulant action of substance P in guinea pig ileum and on blood pressure. Although CX produces no analgesia of itself, it is able to potentiate the analgesic effects of morphine in mice and men. The patent 'invention' describes the effect that CX has an interrupting heroin addiction.

Because of the indole moiety common to serotonin and hallucinogens, there has been a considerable effort spent trying to find relations between 5-HT and hallucinogens. The blocking of 5-HT uptake in platelets by hallucinogens is not specific since many other compounds have the same effect. CX does enhance the potentiation of 5-HT in hexobarbital hypnosis. CX does not bind to 5-HT binding sites in brain. In rats a large dose of 5-HTP and a MAO inhibitor which will raise brain 5-HT levels can mimic the excitation produced by CX and other hallucinogens.

Because most of the studies performed with compound X occurred before 1970, the basic biochemical studies have not been done. Aside from attempts to relate CX and similar drugs to 5-HT there are few reports of effects of CX on neurochemical aspects. This is true of all hallucinogens, not only C-X.

The conclusions of this study of the literature is that compound-X is a typical hallucinogen producing an 'alerting' response that develops into excitation, convulsions and hallucinations at higher doses. CX is related to narcotic drugs by its potentiation of opiate-induced analgesia and by its actions in antagonizing the action of Substance P on g.p.i., similar to those of morphine. There is nothing in this literature to suggest that compound-X would have an effect on heroin addiction. There is nothing in this literature to preclude such an effect either. The difficulty is that so little is known about the biochemistry of the addictive state.

It is generally thought that the initial dose of an opioid produces severe depression of autonomic processes and of mental and physical responses and reduced reaction to external and internal stimuli. The brief moment of excitement following i.v. administration, the 'high' is followed by the depressed state. Chronic opioid use leads to a tolerance to many effects but not to the desirable decreased anxiety. Presumably, a

highly tolerant individual, has an unnatural neurochemical and neurohormonal balance maintained by chronic drug exposure. Hypothetically, the effect that an excitant hallucinogen would produce in such a depressed individual could be explosive, a reversal of all of the changes of tolerance, to induce the 'alerting' response. There is nothing in the literature, however, upon which a hypothesis such as this could be based. One small bit of their evidence relating opiate and C-X effects is that of the effect on Substance P. It is generally thought that Substance P has a permissive effect - it allows nerve impulses to flow and neurotransmitters to be released. The endogenous opiopeptides, the enkephalins, have an inhibitory regulatory action. They prevent impulse transmission and neurotransmitter release. Thus, the actions of CX in antagonizing the actions of Substance P, are similar to the effects of endogenous opioids.

#### D. Analysis of Project on Compound-X

There are serious deficiencies in the literature on compound-X supplied to me. There is no data on its toxicity in man. Since the drug was on the market such data must be available. I would not be able to recommend a clinical trial of C-X without good information on its effect in normal man, in hypertensives, in schizophrenics, and on hyperexcitable persons. I would not be able to recommend a clinical trial of CX without knowing that a physician well versed in the effects of CX is standing by with suitable antidotes (atropin, amobarbital, librium are suggested by the literature review).

There are also serious deficiencies in the reports in the patent application. There is no information on the setting in which the trials took place and no information on the presence of a physician at the trials. There seems to be little in the way of protocol in these trials. There is little description of the first stage of CX effects. Did all the patients hallucinate? Did they have tremors or convulsions? Was there any animal experimental results like the second 'high energy' phase of the response to CX? I suggest that double-blind tests be the only ones considered in the future. Blood pressure should be monitored and behavior recorded.

There are also serious deficiencies in the literature concerning basic mechanisms of action for CX. These data probably do not exist in part because interest in the mechanism of action underlying hallucinogenic action has been desultory. Therefore, it is not possible to make any definitive statement about the relationship between opiates and compound-X. It should be mentioned that many therapeutic successes arise empirically and not a a result of a well defined research program.

I believe that further inquiry into the nature of the effect of CX in addicts is worth pursuing. It must be realized that success in treating 5 out of 7 patients is a shaky basis upon which to build a treatment program. More information of the safety of using CX in man should precede treatment study. A small group of patients receiving CX should indicate whether the results of the earlier studies are reproducible. I make the recommendation of further studies not on the basis of documentation in the literature that there is a valid reason for supposing that a hallucinogen can disrupt addictive behavior, but because all possible treatment modes should be investigated.

*Don H. Clout*

EXHIBIT A

Description of Documents and  
Information Disclosed

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