CLINICAL STUDY ON THE PSYCHOTROPIC EFFECTS
OF CAERULEIN
— AN OPEN CLINICAL TRIAL IN CHRONIC
SCHIZOPHRENIC PATIENTS —

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ABSTRACT

An open clinical trial of caerulein diethylamine, a cholecystokinin analogue, was performed in a total of 58 chronic schizophrenic patients maintained on drugs such as antipsychotic agents without dosage modification. The neuro-peptide medication by intramuscular route produced a clinical improvement in 20 cases and was eventually assessed to have been of therapeutic value in 23 cases. Clinical responses to the medication observed in the present series included: subjective changes in mood mostly to become feeling "fine" or "refreshed in the head", improvement in contact, increased spontaneity and objective behavioral changes such as restlessness and excitement. These features of clinical responses observed in respect of mental condition seem to indicate that the drug affects emotion and exerts an analeptic effect as its principal clinical effects. The clinical effects were remarkably long sustained for 1-2 weeks after a single i.m. dose in most responders. Feeling of facial warmth and lassitude as well as symptoms of the gastrointestinal system were encountered as attendant symptoms in 6 cases.

INTRODUCTION

Recently, a number of neuropeptides have been discovered and studies of their effects on the central nervous system are in progress. Among them is cholecystokinin (CCK), a hormone secreted from the duodenal mucosa discovered in 1928 by Ivy and Farrell and known to initiate contraction of the gallbladder and stimulate secretion of pancreatic juice. In 1971, Jorpes and Mutt¹ first deter-

mined its structure being a peptide (CCK-33) composed of thirty-three amino acids. With the progress in research techniques including radioimmunoassay, other cholecystokinins have subsequently been discovered in the intestinal tissues and brain of various species of animals, i.e. CCK-39² containing six additional amino acids at the N-terminal, CCK-12³ consisting of twelve C-terminal fragments, CCK-8^{4,5} comprising eight C-terminal fragments, and CCK-4⁶ composed of four C-terminal fragments. Of these CCK analogues, practically equal amounts of CCK-8 and CCK-33 occur in the intestinal mucosa, while it has been described that, in the brain, virtually all substance immunoreactive for CCK is the octapeptide cholecystokinin.^{2,7,8} A study of Saito *et al.* in which the affinity of CCK-8 and CCK-3 for cholecystokinin receptors in the rat was measured,⁹ demonstrated a greater affinity of CCK-8 for receptors in the pancreas and in the brain (approximately three-fold) as compared to CCK-33. The distribution of CCK in various regions of the brain has been investigated notably by Rehfeld² and Schneider *et al.*¹⁰ According to their reports, rat and porcine cerebral cortices contain, remarkably high concentrations of CCK, more than ten times as high as cerebrocortical levels of other neuropeptides. Next to its occurrence in the cerebral cortex, CCK was demonstrated at the highest concentration in the olfactory bulbs, followed, in order, by the corpus striatum, hypothalamus, hippocampus and mesencephalon, but none in the cerebellum.

Of various CNS effects of CCK-8, one which has long been believed to exist is an effect of giving rise to feeling of satiety. It is attributable, according to Itoh *et al.*,¹¹ to an action of this hormone upon the ventromedial nucleus of the hypothalamus. It has also been reported by Itoh *et al.*¹² that CCK-8 injected into the lateral ventricle of rat brain produced enhancement of pentobarbital-induced sleep, suppression of spontaneous motor activity evoked by TRH or methamphetamine, a hypothermic response, and inhibition of reactions to L-dopa. In other experimental studies, the investigators observed that CCK-8 inhibited catalepsy evoked in rats by administration of β -endorphin.¹³ Meanwhile, Hökfelt *et al.*^{14,15} and Snyder¹⁶ discovered coexistence of CCK and dopamine (DA) in neurones of the ventral tegmental area of rat brain, or A10 of Dahlström and Fuxe.¹⁷ The DA-neuronal system of this region of the brain has recently been acquiring importance in connection with etiology of schizophrenia and actions of psychotropic drugs.

In a behavioral-pharmacologic study of Zetler¹⁸ conducted on mice and rats, CCK-8 and caerulein, a CCK analogue, were found to be endowed with a diazepam-like anticonvulsant effect and with haloperidol-like cataleptogenic effect and effect of suppressing stereotypic behavior when administered by peripheral routes; the effects being more conspicuous than those of diazepam and haloperidol. The investigator inferred from the findings that both peptides might be a sort of

Cholecystokinin triacontatriapeptide (CCK-33) Caerulein decapeptide (CLN) Cholecystokinin octapeptide (CCK-8)

Fig. 1 CCK Analogues.

brain-protective substances characterized by an anorexigenic, rather than orexi-genic, property as tranquilizers as well as by lack of convulsant action as neuro-leptics. Caerulein is a decapeptide structurally remarkably analogous to the C-terminal of CCK (Fig. 1). It was isolated from the skin of Australian frog, *Hyla caerulea*, and has not been found in any mammalian species. This sub-stance has been noted to exert CNS effects comparable to those of CCK-8 in the foregoing experiments of Itoh et al. and Zetler; it has proven to be far more potent than CCK-8 in respect for the CNS effects.

Moroji et al.^{19,20} performed a clinical trial of caerulein diethylamine in 20 patients with chronic schizophrenia, on the grounds of the aforementioned experi-mental data. With dosage of 0.3 to 0.6 $\mu\text{g/kg}$, the treatment produced improve-ment of such symptoms as emotional disturbances, autism and auditory hallucina-tion in 16 patients and caused little or no side reactions. Recently, we had the opportunity of clinically trying an injectable preparation of caerulein diethyl-amine in a noticeable number of chronically schizophrenic patients with voluntary consent of them and their families. This report documents the results.

SUBJECTS AND METHODS

Fifty-five chronic schizophrenic patients, 46 hospitalized and 9 ambulatory, were treated in this study at the affiliated hospitals where the authors were working. They had been failing to respond with marked improvement to various treatments over long periods, mostly with a duration of illness of more than 5 years. There were 31 men and 24 women ranging in age from 20 to 62 years, with a mean age of 37.2 ± 9.5 years.

The injectable preparation of caerulein diethylamine (CLN) is currently used a medical diagnostic agent in this country. In view of the present purpose

Table 1 *Psychiatric rating scale*

			×	—4
1	Abnormal behaviour (Motor disturbances)	Decrease of movement (Motor retardation)		No movement or reaction whatever when approached (stupor, catalepsy)
		Increase of movement (Motor excitement)		Extreme excitement or agitation, continuously
		Unnatural action or behavior	Impulsive acts, talks to self, unusual incli negativism, wandering, uncleanly action	Marked and continuous
2	Abnormality in speech or talking	Scanty		Silent even when addressed
		Talkative		Talkative, can not control it
3	Disturbance of thought		There may be but can not be confirmed	Can not grasp the meaning at all
4	Rapport			No rapport
5	Contact (attitude toward other persons)			Completely autistic, indifferent and negativistic; no response when addressed
6	Abnormality of feeling	Expression of feeling		Emptiness, completely no emotional response
		Disturbance of other feelings		Marked Anxiety, tension, irritable, changeable
7	Hallucination and disturbance of self-consciousness		It may be present but can not be confirmed.	Severe and everyday life is always governed by it.
8	Delusion (delusional perception, delusional conception, delusional mood, etc.)		It may exist but not confirmable	Has confidence. For this reason everyday life is disturbed.

for schizophrenia (for Doctor's use)

-3	-2	-1	0
Barely reacts or move when approached but no movement when left alone	Moves or reacts even when not approached but does not do anything definite or concrete.	Can do things coherently but not sufficiently positive	None
Moderate excitement or agitation, intermittently	Uneasy or unsteady actions	Somehow restless or fidgety	None
Moderate nation to smile or laugh, eccentricity, stereotype,	Mild	Stiff expression, somehow unnatural attitude	None
Barely opens mouth to speak when addressed	Talks spontaneously but reticently, and only when necessary	Seems somewhat scanty of words	
Talkative but can control it	Talkativeness not conspicuous but talks unnecessarily	Seems somewhat talkative	
Can grasp the meaning incompletely	There is a meaning but the association is weak and there is flight in thought	There is no weakness in association or flight of thought but the entire coherence is poor	
Can be understood somehow but incompletely. Only response of indistinct meaning (much eccentricity may impulsive acts)	Response does not conform to the other person, unnatural and slow or dull (childish, meagre in content, nonchalance, indifferent, shameless, rude, unreserved, etc.)	Can respond well but there is a slight abnormality (no luster or will power, no quick response, mild unnaturalness)	
Responds when addressed; when left alone autistic, indifferent or negativistic with no contact with other persons; unrealistic behavior.	Has the usual contact with other persons but apt to be isolated; indifferent to surroundings or negativistic; especially has tendency to avoid people.	Retains contact with other persons but is passive and does not contact other people actively.	
Very few	Meager	Somewhat meager	Sufficient
Quite marked depression, exhilaration, exaltation, quick tempered,		Very mild, not continuous even if present	None
Milder than (-4) and everyday behavior is at times governed by it.	Is definitely present but is not of the degree to govern everyday behavior.	Is of mild degree; of uncertain degree; appears and disappears	None
Has confidence. However, everyday life is not disturbed.	Half in doubt	Understands tentatively when explained.	None

Table 1 *Continued*

		×	—4
9	Complaint of hypochondria or neurotic complaints		Severe and governs the entire everyday life
10	Insight into disease	Difficult to judge	Completely governed by it. Indifferent.
11	Keeping oneself neat and tidy (clothing, food, etc.) Evaluate by the item showing the worst result.		Can not do anything by himself
12	Work or recreation		Does not anything, non-chalant or negativism

Table 2
Clinical global impression

<u>General improvement rating (GIR)</u>	
0—Unassessable	4—Unchanged
1—Markedly improved	5—Slightly worsened
2—Moderately improved	6—Worsened
3—Slightly improved	7—Seriously worsened
* Evaluate each patient for degree of changes evoked by treatment (drug) in his (or her) clinical manifestations throughout the study.	
<u>Overall safety rating (OSR)</u>	
1—No side-effects	
2—Mild side-effects	
3—Side reactions necessitating dosage reduction	
4—Side reactions leading to discontinuation of medication	
* Rate the patient as to safety of therapy regimen in the gross, encompassing the types, incidence, degree and duration of side-effects or complications that developed in the course of study treatment as well as treatment undertaken, if any, for them.	
<u>Global utility rating (GUR)</u>	
1—Very useful	5—Slightly undersirable
2—Fairly useful	6—Fairly undersirable
3—Slightly useful	7—Very undersirable
4—Not appreciably useful	
* Evaluate the treatment (drug) as to whether it has been of value for the patient throughout the study, syntherically on the grounds of general improvement rating, side-effects, etc.	

-3	-2	-1	0
Adheres to it and continuously complains but not of the degree to govern the entire everyday life.	Always complains but no disturbance of everyday life	Mild but appears and disappears	None
Convinced he is normal	Is able to make comments or criticisms partially if instructed so.	Is able to make comments or criticisms if instructed so. In general, insight into disease exists	Insight into disease sufficiently exists
Can prepare for a meal and also easily dirties the clothing	When cautioned does it himself; no necessity for assisting.	Does only his own things by himself.	
Finally does it when told to do so.	Does it himself but does not continue long and soon tires.	Positiveness insufficient but does it normally.	

of its application as a psychotropic agent for schizophrenic patients, the treatment was carried out as open trials with the voluntary consent of patients and their families.

CLN was administered intramuscularly in doses of 20 μg (one ampule) or 40 μg (two ampules). Each patient received one or two doses with an interval of one week or more between them as a rule. The interdose interval and total number of doses to be given were determined by the attending physician and there were 5 patients who received three or more doses. The medication was performed in combination with the antipsychotic and other drugs which the patient had been receiving, without modification of their dosage during the study. The attending physician interviewed each patient at 2-3 hours, 3 days, and 1, 2 and 3 weeks after administration to assess the patient's condition on the Brief Psychiatric Rating Scale (BPRS) as well as to detect adverse reactions. Evaluation by the Keio University Psychiatric Rating Scale for Schizophrenia (Keio Univ. R. S.) (Table 1) was also made at the same time in some of the cases. At the final interview of the clinical trial, the physician made, in addition, the general improvement rating (GIR), overall safety rating (OSR) and global utility rating (GUR) (Table 2) on each patient and descriptive records as comments on alterations in mental state and attendant symptoms observed during the study treatment. Of the 55 patients studied, 3 received two separate courses of CLN therapy more than one month apart. Besides, one patient with affective psychosis (depressive state) also received CLN in the study.

RESULTS

Changes in Total Score on BPRS in A 11 Treated Patients:

Total scores on BPRS at periods following medication and GIR, OSR and GUR scores of all patients are shown in Tables 3 to 7, where a total of 59 cases treated are listed according to sex, age and dosage. Of the total of 58 cases of chronic schizophrenia, 20 cases were "improved" (GIR: 1-3) (markedly improved, 1 case; moderately improved, 2 cases; slightly improved, 17 cases), 34 cases "unimproved" (GIR: 4), and 4 cases "slightly worsened" (GIR: 5). Of the 20 improved cases, 6 cases received a single dose (out of 31 cases) and 14 received repeated doses (out of 27 cases); hence the greater number of improved cases on repeated dosage. However, the improvement was evident already with an initial dose in all these 14 cases given repeated doses and it was not that the improvement occurred only after repeated doses. It appears that the dosage was repeated in a considerable proportion of these cases because

Table 3
Changes in total score on BPRS in all treated patients.—1
(Patients given a single dose of 1 ampule)

Case No.	Sex	Age	Dose	Total Score on BPRS						Clinical Global Impression		
				0 hr	3 hrs	3 days	1 wk	2 wks	3 wks	GIR	OSR	GUR
1	M	27	1A	54	53	52	52	54	54	4	1	4
2	M	35	1A	35			36	30	33	4	1	4
3	M	40	1A	40	39	37	40	42	42	3	2 ⁺⁺⁺	3
4	M	43	1A	55	53	44	55	50	47	4	1	4
5	M	49	1A	42		42	42	36	36	4	1	4
6	M	51	1A	53	53	51	52	40	43	4	1	4
7	M	53	1A	33			33	33	34	5	2 ⁺	5
8*	F	30	1A	61		56	58	55		3	1	3
9	F	34	1A	45	45	45	45			4	1	4
10	F	36	1A	59	59		50	53	53	4	1	4
11	F	45	1A	82	82	84	69	63	65	5	1	5

Legends for Tables 3 to 7:

* : The patient received CLN therapy on two separate occasions more than one month apart.

** : Manic-depressive psychosis (depressive state).

*** : The patient received doses with the interval or intervals in parentheses, as an exceptional case.

+ : The patient developed an attendant symptom or symptoms of the gastrointestinal system.

++ : The patient developed feeling of facial warmth as an attendant symptom.

+++ : The patient developed lassitude as an attendant symptom.

Table 4
Changes in total score on BPRS in all treated patients.—2
(Patients given a single dose of 2 ampules)

Case No.	Sex	Age	Dose	Total Score on BPRS						Clinical Global Impression		
				0 hr	3 hrs	3 days	1 wk	2 wks	3 wks	GIR	OSR	GUR
12	M	22	2A	38			39	38	25	4	2 ⁺⁺	4
13	M	24	2A	61	61	59	59	61	61	4	1	4
14	M	26	2A	46				36	33	3	1	3
15	M	29	2A	43	40	40	25	39	29	3	1	3
16	M	31	2A	42				37		3	1	3
17	M	33	2A	61	38	36	32	32	33	2	1	2
18	M	34	2A	35	35	35	35	35	35	4	1	4
19*	M	35	2A	34		31	34	30	35	4	2	3
20	M	40	2A	37	37	37	37	37	37	4	1	4
21	M	43	2A	47	48	48	48			4	1	4
22	F	21	2A	82	82	73	73	73	73	4	1	4
23	F	30	2A	59		61	61			4	1	4
24	F	32	2A	68	65	69	69	68	68	4	1	4
25*	F	35	2A	78	78	78	78	78	78	4	1	4
26	F	35	2A	28			23	24	26	4	1	4
27	F	42	2A	69	69	69	69	69	69	4	1	4
28	F	43	2A	34			31	24	23	5	2 ⁺⁺⁺	5
29	F	44	2A	61	62	61	61			4	1	4
30	F	50	2A	30			28	28	24	4	1	4
31**	F	50	2A	34				34		4	1	4
32	F	63	2A	68	68	59	57	56	63	4	1	4

the physician noted usefulness of the medication after the first dose. As for interrelation of the dosage and therapeutic response, "improvement" occurred in 9 of the 24 cases after an initial dose of 20 μ g (1 ampule) and in 11 of the 34 cases after that of 40 μ g (2 ampules). From the present data, it seems to be that it cannot be concluded the dosage of 40 μ g (2 ampules) was more effective than that of 20 μ g (1 ampule).

Comparison of Background Between Improved and Unimproved Case Groups:

The distribution of patient characteristics between the group of cases improved and that of cases unimproved is summarized in Tables 8 and 9. The mean age of the improved group (34.3 ± 6.3 years) was significantly lower than that of the unimproved group (38.8 ± 10.6 years) ($0.01 < P < 0.05$). Patients with durations of hospitalization over 10 years were more frequent in the unimproved group. There was no noticeable intergroup difference in any other respect.

Initial (Pretreatment) BPRS Profile:

Table 5

Changes in total score on BPRS in all treated patients.—3
(Patients given two doses, 1 ampule initially and 1 or 2 ampules later)

Case No.	Sex	Age	Dose	Total Score on BPRS						Clinical Global Impression		
				0 hr	3 hrs	3 days	1 wk	2 wks	3 wks	GIR	OSR	GUR
33	M	30	1A	66	61	48	68					
			1A	60	58	55		47		3	1	3
34	M	30	1A	61	58	57	52					
			1A	52	52	52	51	52		3	1	3
35	M	31	1A	47	46	47	47					
			1A	47	47	47	47			4	1	3
36	M	36	1A	59	59	58	58	59				
			1A	59	59					4	1	3
37	M	42	1A	37	35	34	36					
			2A	36	34	34	36	36		3	1	3
38	M	45	1A	56	49	49	50	50	55			
			1A	51	49	50	50	50	50	3	1	3
39	F	20	1A	55	55	55	55					
			2A	55	55		53	57		4	2 ⁺	4
8*	F	30	1A	57	57	56	46	52				
			1A	52			50			1	1	3
25*	F	32	1A	65	65	65	65					
			1A	65	64	64	64			4	1	4
40	F	32	1A	72			72					
			2A	72			66			3	1	3
41	F	44	1A	57	57	61	57					
			1A	57			52	52		4	1	4

Figure 2 illustrates the profiles of average BPRS scores of the improved and unimproved case groups at the initiation of study treatment. As can be seen, there was no significant intergroup difference in total or itemized scores but the improved case group appears to show generally high scores.

BPRS Score Changes in the Improved Case Group:

As noted in Tables 3 to 7, maximal change (improvement) of scores on BPRS occurred within one week after dose in virtually all improved cases. Table 10 shows the changes in mean BPRS score of 15 cases with complete pertinent data at 0 hour (pretreatment), 2-3 hours, 3 days and 1 week after the first dose. The total score and practically all items revealed a tendency to gradual decline over the one-week period following medication, but neither the total score nor any item showed significant difference between 0 hour and 1 week.

In Figure 3, the profiles of average BPRS scores of 20 improved cases at

Table 6
Changes in total score on BPRS in all treated patients.—4
(Patients given two doses of 2 ampules each)

Case No.	Sex	Age	Dose	Total Score on BPRS						Clinical Global Impression		
				0 hr	3 hrs	3 days	1 wk	2 wks	3 wks	GIR	OSR	GUR
42	M	31	2A	75	70	72	72					
			2A	72	72	72	72	72	75	3	1	3
43	M	32	2A	50	50	50	49					
			2A	49	49	38	38			4	1	4
44	M	33	2A	80	80	80	80					
			2A	80	77	77	78			4	1	4
19* *** (4D)	M	35	2A	34			41					
			2A							5	1	5
45	M		2A	69	69	69	69					
			2A	69	69	69	69			4	1	4
46	M	57	2A	56	56	56	56					
			2A	56	56	56	56	56	56	4	1	4
47	M	59	2A	36	36	36	36					
			2A	36	34	35	35			4	1	4
48	F	31	2A	34			33	37	35			
			2A							4	1	4
49	F	35	2A	53	63	48	50					
			2A	50	60	47	53			3	1	3
50	F	39	2A	64	59	60	60					
			2A	61	61	64	64	64	64	3	1	3
51	F	48	2A	36		31	28					
			2A	28			28			3	1	3

0 hour (pretreatment) and at periods with maximal decrease in total score are shown. Significant improvement was noted in respect of Item 1 (somatic concern: $0.01 < P < 0.05$), Item 2 (anxiety: $0.01 < P < 0.05$), Item 3 (emotional withdrawal: $P = 0.01$), Item 13 (motor retardation: $0.01 < P < 0.05$), Item 14 (uncooperativeness: $0.01 < P < 0.05$) and total score ($P = 0.01$).

Figure 4 is the plot of changes in BPRS-contrast function based on the data in Figure 3. It failed to reveal any characteristic tendency to clinical improvement.

Initial (Pretreatment) Keio Univ. R. S. Profile:

The profiles of initial average scores on Keio Univ. R. S. in 10 cases from the improved group and 18 from the unimproved group with pertinent rating data are compared in Figure 5. No significant intergroup difference could be observed in respect of total score or any itemized average score. Moreover, there

Table 7
Changes in total score on BPRS in all treated patients.—5
(Patients given three or more doses)

Case No.	Sex	Age	Dose	Total Score on BPRS						Clinical Global Impression		
				0 hr	3 hrs	3 days	1 wk	2 wks	3 wks	GIR	OSR	GUR
52	F	24	1A	51	51	51	51					
			1A	51			51					
			1A	51			51			3	2+	3
53	M	27	2A	36	35	41	37					
			2A	37	41	36	41	31				
			2A	31	34	36				3	1	3
54	M	51	2A	28			29					
			2A	29			32					
			1A	32			28			4	1	4
55	F	36	1A	74	76	68	69	63				
			1A	63	62	62	60	63	63			
			2A	63	64	64	64	64	63			
			2A	63	67	63	65	65	65	3	1	3
56	F	28	2A	75	69	74	61	58				
			*** (10D)	1A	58			43				
			*** (10D)	1A	43		38					
			1A	38			38					
			1A	38			33			2	1	2

was no tendency for the scores to be generally higher in the improved group by BPRS.

Table 11 shows the total and itemized average scores on the Keio Univ. R. S. at 0 hour (pre-treatment), 2–3 hours, 3 days and 1 week after dose in 8 cases with complete pertinent data among the 10 improved cases in Figure 5. The scores were generally prone to decrease gradually but neither the total score nor any itemized score showed significant difference between 0 hour and 1 week after administration.

Changes in Mental Condition as Stated in the Physician's Comment:

Most frequently observed in the present series were subjective changes of mood, viz., the patient became to "feel fine", "relieved of heavy-headedness", or "feel refreshed in the head". These changes occurred in 12 of the total of 58 cases (Nos. 14, 15, 18, 29, 32, 35, 36, 37, 38, 49, 50 and 56). Ranking next in frequency to them was improvement of contact in the broad sense of the term, such as improved attitude toward other persons and improvements in respect of ill-temperedness, hostility and uncooperativeness; these were evident in 11 cases (Nos. 8, 33, 34, 38, 8, 40, 42, 50, 52, 55 and 56). In the third place, in-

Fig. 2 BPRS profiles at initiation of clinical trial.
(Mean values in respective groups)

—●— GIR < 4 (n=20): Mean of total scores: 55.3 ± 13.5
 -○- GIR ≥ 4 (n=38): Mean of total scores: 51.5 ± 16.2

crease of spontaneity evidenced by the statements that the patient became "to do work in the ward", "capable of performing routine household matters", or "somewhat talkative" was observed in 7 cases (Nos. 32, 34, 37, 47, 53, 55 and 56). Diminution of hallucination and delusion occurred in 5 cases (Nos. 3, 8, 49, 52 and 56), improvement of mannerism in 3 cases (Nos. 8, 8 and 42) and that of attentiveness in 2 cases (Nos. 3 and 37). While all these changes were desirable responses, so to speak, undesirable responses were also noted in 6 cases. They were almost invariably such objective behavioral changes as excitement and restlessness. These changes were diverse in degree, ranging from alterations in attitude or facial expression accompanied by mere complaints of feeling "irritated" or "elligerent" to insomnia, use of violence or demolition of properties in

Table 8
Background of 19 improved cases (GIR: 1-3) and 36 unimproved cases (GIR: 4-7). I

	Improved (19 cases)		Unimproved (36 cases)	
	11 males and 8 females		20 males and females	
Sex				
Age*	26 to 48 years; average, 34.3±6.3 years		20 to 62 years; average, 38.8±10.6 years	
Age at onset	14 to 34 years; average, 19.8±4.9 years		14 to 46 years; average, 22.3±7.0 years	
Duration from onset till present	>10 years: 17 cases	3 to 5 years: none	>10 years: 28 cases	3 to 5 years: 2 cases
	5 to 10 years: 1 case	2 to 3 years: 1 case	5 to 10 years: 4 cases	2 to 3 years: 2 cases
Duration of present hospitalization	>10 years: 3 cases	1 to 2 years: 1 case	10 years: 13 cases	1 to 2 years: 5 cases
	5 to 10 years: 3	<1 year: 2	5 to 10 years: 5	<1 year: 3
	3 to 5 years: 6	Ambulatory: 4	3 to 5 years: 3	Ambulatory: 5
	2 to 3 years: none		2 to 3 years: 2	
Type of schizophrenia	Hebephrenia	10 cases	Hebephrenia	19 cases
	Catatonia	1	Catatonia	6
	Paranoid form	5	Paranoid form	9
	Hebephrenic-catatonica	1	Hebephrenic-catatonica	1
	Hebephrenic-paranoid	1	Unclear	1
	Catatonic-paranoid	1		
Number of recurrences	≥5 times: 4 cases	Twice: 2 cases	≥5 times: 11 cases	Twice: 9 cases
	4 times: 2	Once: 4	4 times: 3	Once: 5
	3 times: 6	Unclear: 1	3 times: 0	Unclear: 8

* A significant intergroup difference at $0.01 < P < 0.05$ (Z-test).

Of the 55 patients subjected, three (Case No. 8, 19, 25) received separate courses of CLN therapy several month apart, and improvements on both regimen were shown in Case No. 8. Considering these two separate regimen on each three cases as two different treatment occasions, number of total treatment cases and of improved cases were calculated at 58 and 20 in data analysis as described in Results and Fig. 2.

Table 9

Background of 19 improved cases (GIR: 1-3) and 36 unimproved cases (GIR: 4-7). II

Clinical picture			
Excitement	2 cases	Excitement	4 cases
Stupor	1	Stupor	2
Hallucination & delusion	9	Hallucination & delusion	12
Delusion	1	Lack of spontaneity & apathy I	1
Lack of spontaneity & apathy I	1	Lack of spontaneity & apathy II	16
Lack of spontaneity & apathy II	5	Depressive state	1
Type of clinical course			
Acute deteriorated	1 case	Unclear	3 cases
Chronic deteriorated	5	Acute deteriorated	2
Chronic defective	9	Chronic deteriorated	10
Periodic deteriorated transitional	1	Acute defective	2
Periodic defective transitional	2	Chronic defective	10
Periodic complete abatement	1	Periodic deteriorated transitional	4
		Periodic defective transitional	5
Somatic treatment			
Drug alone	10 cases	Drug alone	22 cases
Drug plus E.C.T.	9	Drug plus E.C.T.	14
Type of ward			
Closed	14 cases	Closed	28 cases
Open	1	Open	3
Ambulatory	4	Ambulatory	5
Precipitating factor(s)			
None	13 cases	None	21 cases
Present	3	Present	6
Not clear	3	Not clear	9

the ward thus necessitating injections of antipsychotic drugs or accommodation of the patient in a safeguarding room.

The time-course of changes in mental condition seen in the patients was as follows: Changes of mood characterized by the patient's depiction: "feeling fine" or "feeling refreshed in the head", or behavioral alterations to excitement and restlessness developed first by 15-30 minutes to 3 days after administration of CLN. It was then followed by improvement of what are called schizophrenic symptoms such as improvement of contact, increase of spontaneity, abatement of hallucination and delusion, alleviation of mannerism and improvement of attentiveness. These changes disappeared in 3 days to 3 weeks after the final dose, or lasted in nearly all cases for 1-2 weeks after the final dose.

Physicians' comments on the therapeutic responses in 5 (Nos. 8, 35, 37, 8 and 53) of those cases receiving repeated doses of CLN in a single course or

Table 10
*Changes in mean score on BPRS in a group of patients showing improvement
 (GIR: 1-3), following the first dose. (N=15)*

Items	0 hr	2 hrs	3 days	1 wk
1 Somatic Concern	2.5	2.2	1.9	1.7
2 Anxiety	2.4	2.1	1.9	2.1
3 Emotional Withdrawal	4.4	3.7	3.7	3.8
4 Conceptual Disorganization	4.5	4.7	4.4	4.3
5 Guilty Feelings	1.4	1.4	1.4	1.3
6 Tension	2.9	2.8	2.7	2.5
7 Mannerisms and Posturing	4.4	4.2	4.2	3.9
8 Grandiosity	1.9	1.8	1.9	1.7
9 Depressive Mood	1.8	2.0	1.7	1.7
10 Hostility	2.7	2.5	2.2	2.2
11 Suspiciousness	2.7	2.7	2.6	2.7
12 Hallucinatory Behavior	4.1	4.1	3.9	3.7
13 Motor Retardation	3.8	3.1	3.1	3.1
14 Uncooperativeness	3.7	3.1	3.0	3.1
15 Unusual Thought Content	4.9	4.9	4.4	4.2
16 Blunted Affect	4.7	4.5	4.5	4.3
17 Excitement	2.5	2.4	2.4	2.3
18 Disorientation	1.5	1.5	1.5	1.5
Total	56.6	53.4	51.4	50.0

undergoing two separate courses more than one month apart included statements purporting to imply that therapeutic responses to second and subsequent doses were less conspicuous than those to an initial dose. Conversely, it was stated in no case that later doses brought about more pronounced therapeutic effects than the initial dose even when the dosage was increased after the first, or otherwise.

Of the three cases in which the CLN therapy was carried out on two separate occasions with an interval of more than one month between them, Case No. 8 received 20 μ g of CLN on each occasion. The physician's comment on the clinical response of this patient was that the effect of the second medication was not so conspicuous as that of the first. The patient of Case No. 19 received 40 μ g on both occasions; the patient became to complain of "feeling irritated" 2 hours after the first medication and 4 days after the second medication, respectively. The excitement was more pronounced on the second occasion in this case to such an extent that injections of an antipsychotic drug were required for its control. In Case 25, neither the first medication nor the second produced any appreciable response though at different dose levels.

There were 3 patients who were discharged home during the study period (Case Nos. 15, 33 and 56). The dismissal from hospital was apparently ascribable

Table 11

Changes in mean score on Keio Univ. Psychiatric Rating Scale for Schizophrenia in a group of patients showing improvement (GIR: 1-3), following the first dose. (N=8)

		0 hr	3 hrs	3 days	1 wk
1	Abnormal behaviour (Motor disturbances)				
	Decrease of movement (Motor retardation)	2.4	2.4	2.1	2.1
	Increase of movement (Motor excitement)	2.5	2.4	2.5	2.1
	Unnatural action or behavior	3.6	3.4	3.1	3.0
2	Abnormality in speech or talking				
	Scanty	2.5	2.1	2.1	2.1
	Talkative	1.5	1.6	1.6	1.4
3	Disturbance of thought	3.8	3.6	3.4	3.3
4	Rapport	3.1	3.0	2.8	2.8
5	Contact (attitude toward other persons)	3.3	3.0	2.6	2.6
6	Abnormality of feeling				
	Expression of feeling	3.4	3.1	2.9	2.9
	Disturbance of other feelings	2.8	2.6	2.6	2.5
7	Hallucination and disturbance of self-consciousness	3.4	3.4	3.4	3.3
8	Delusion (delusional perception, delusional conception, delusional mood, etc.)	3.5	3.5	3.5	3.1
9	Complaint of hypochondria or neurotic complaints	2.1	1.9	1.8	1.6
10	Insight into disease	4.0	3.8	3.8	3.6
11	Keeping oneself neat and tidy (clothing, food, etc.) Evaluate by the item showing the worst result.	2.6	2.6	2.4	2.4
12	Work or recreation	4.1	4.1	3.9	3.5
Total score		48.5	46.5	44.4	42.3

to clinical improvement by the CLN therapy in one case (No. 56). The patient, discharged home two weeks after the first dose, has been maintained on CLN, 20 μ g weekly. Dosage reduction of anti-psychotic drugs has become practicable in the case, possibly owing to it. No appreciable clinical improvement occurred in the case of manic depressive psychosis (depressive state; No. 31).

Side-Effects:

There were 6 patients who developed during the CLN clinical trial so-

Fig. 3 BPRS profiles at initiation of clinical trial and at the time of maximal clinical improvement. (Mean values of 20 patients)

* Items for which significant differences were noted: # 1, 2, 13 and 14
($0.01 < P < 0.05$); and # 3, total score ($P = 0.01$) by Z-test.

●—● Prior to 1st dose: Mean of total scores: 55.3 ± 13.5

○---○ At maximal improvement: *Mean of total scores: 44.6 ± 13.1

Table 12

Attendant symptoms possibly attributable to CLN medication

Gastrointestinal symptoms:
anorexia, nausea, abdominal malaise, increased frequency of defecation, diarrhea, and hematochezia (?)
Symptom arising from increased vascular permeability:
feeling of facial warmth
Other: General lassitude

Fig. 4 Changes in BPRS-contrast function in improved cases. (GIR < 4, N=20)
(At initiation of trial and at maximal clinical improvement)

matic attendant symptoms apparently attributable to the CLN medication according to judgement by the attending physician. They included nausea occurring 20 minutes after administration (No. 3), anorexia, slight hematochezia and lassitude that developed one week after administration and diarrhea at 2 weeks (No. 7), feeling of facial warmth which persisted over 3 weeks following injection (No. 12), marked lassitude occurring 2 weeks after administration (No. 28), defecation preceded by abdominal distress 15 minutes after a second dose (No. 39) and increased frequency of defecation on the day of administration (No. 52) (Table 12). An antidepressant was administered to the patient of Case No. 28 because of marked feeling of fatigue; the patient recovered in a few days. In the remaining 5 cases, signs or symptoms of unwanted effects disappeared spontaneously without any particular treatment. In no case did extrapyramidal symptoms (EPS) or their modifications occur throughout the study.

Evaluation of Usefulness:

The CLN therapy was rated as "useful" (GUR: 1-3) in 23 of the total of 58 cases of chronic schizophrenia treated. Of these 23 cases, 20 cases had noticeable symptomatic improvement (GIR: 1-3), whereas in the remaining 3 cases (Nos. 19, 35 and 36), no such symptomatic amelioration occurred but the treatment was evaluated as "useful" in consideration of the fact that the patients

Fig. 5 Keio Univ. R. S. profiles at initiation of clinical trial.
(Mean values in respective groups)

●—● GIR < 4 (n=10): Mean of total scores: 49.9 ± 9.2
○---○ GIR ≥ 4 (n=18): Mean of total scores: 51.4 ± 10.4

psychotic and other psychotropic medications on which the patients had been maintained, yet without modification of their dosage. However, changes of mood showed subjective changes to state that they became “to feel fine” or “to feel refreshed in the head”. There were 4 cases in which the CLN therapy was rated as “undesirable” (GUR: 4–7); the evaluation was based on the reasons described under attendant symptoms in 2 cases (Nos. 7 and 28) and in view of the development of excitement and restlessness (GUR: 5) in the other 2 cases (Nos. 11 and 19). The treatment was assessed as “not particularly useful” (GUR: 4) in the remaining 31 cases.

DISCUSSION

It is considered not appropriate to mention much about effects of CLN *per se* in this report inasmuch as the patients admitted to this open clinical trial received CLN in the form of combination treatment with continuation of the antipsychotic and other psychotropic medications on which the patients had been maintained, yet without modification of their dosage. However, changes of mood as described by the patient with the expressions: "I've become to feel fine", or "refreshed in the head" and behavioral changes such as improvement of contact, enhancement of spontaneity, excitement and restlessness were noted commonly in a relatively large proportion of the treated patients and, therefore, might represent effects brought about by the administration of CLN. Comparison of the BPRS profile at the period of maximal improvement with the pretreatment profile in the improved case group revealed a significant improvement in respect of the items concerned with emotion, contact and psychomotor retardation, i.e. (1) somatic concern, (2) anxiety, (3) emotional withdrawal, (13) motor retardation and (14) uncooperativeness. They provide evidence in support of these effects of the drug. None in the present series displayed any noticeable signs of sedation or anti-hallucino-delusional effect, unlike the case of many antipsychotic drugs. When referred to the fact several patients developed hyperexcitability that could be associated with the study treatment, at least a sedative effect seems to be unlikely with CLN. It may be that CLN has properties not so much characteristic of antipsychotic drugs as a psychotropic agent somewhat akin to antidepressants and antianxiety drugs, so far as the compound is endowed with "effects on emotion" and "psychoanaleptic effect" as its principal clinical actions as estimated from the results. No appreciable clinical response occurred in the only case of MDI (depressive state) treated. The above-described clinical effects represent those observed in the patients mostly receiving only one or two doses of 20 or 40 μ g and there exists a possibility that, as in case of certain antipsychotic drugs, CLN may produce other different clinical effects at other dose levels.

Another point of interest concerning CLN is the remarkably long duration of sustained clinical effects. As described above, its effects persisted for 1 to 2 weeks after a final dose in almost all cases in the improved group, and that there were cases in which the influence of CLN medication remained even as late as 3 weeks after injection. Drugs with such a long duration of sustained effect among the psychotropic drugs heretofore introduced are depot preparations of certain medicaments. Can CLN, being a decapeptide and not in the form of depot preparation, really occur undecomposed in the body for more than a week without much loss of activity? The duration of sustained clinical effects seen

in the present series is extremely longer when referred to the reports that effects of CLN on the intestinal tract disappeared in 30-40 minutes after administration²¹ and that the biologic half-life of intravenously injected CCK-33 was determined by radioimmunoassay to be 2.59 and 3 minutes in the dog²² and guinea pig,²³ respectively, and that of endogenous CCK-33 to be 5 to 7 minutes in man.²⁴ The present observation of remarkably long-sustained clinical effects of CLN in a group of chronic schizophrenics would serve as an aid for future attempts to elucidate biodynamics, sites of action and the mechanism of psychotropic actions of CCK analogues.

Somatic attendant symptoms considered apparently associated with the administration of CLN were noted in 6 cases. Those seen in 4 of the cases were transient symptoms of the gastro-intestinal system due to contraction of the gallbladder, stimulation of pancreatic secretion and enhanced intestinal peristalsis which are proper effects of CCK analogues. Erspamer *et al.* reported that CLN exerts a hypotensive effect in various species of animals chiefly by intravenous route,²⁵ and increases capillary vascular permeability to cause papules and feeling of facial warmth in man following intradermal injection,²¹ besides the effects on the digestive organs. According to the report, the hypotensive effect was allayed by atropine and augmented by α -adrenoceptor blockers in dog, suggesting a possible cholinergic activity of the decapeptide toward smooth muscles of the vascular wall. They described that these side reactions occurred in man only at high doses, usually >10 ng/kg i.v., >5 ng/kg per minute by i.v. drip, or >1 μ g/kg s.c. or i.m. None in the present study received greater doses than the upper limits of safe dosage of Erspamer *et al.*, and there is reliable information that the actual content of CLN in the injectable preparation used in the present investigation was only approximately 1/2 of the declared content. It follows that 6 of the 55 chronic schizophrenics developed attendant symptoms after an intramuscular dose of 10 or 20 μ g of CLN in this study. Besides the problem of dosage, the symptoms of the gastrointestinal system seen in 4 of the 6 cases and feeling of facial warmth in 1 case were the types already reported by other investigators while no appropriate explanation can be found at present for the intense feeling of fatigue that developed two weeks after administration in the remaining case. The slight hematochezia reported in Case No. 7 was a complaint of the patient and not confirmed by the attending physician, hence remains unclear. As described under results, the attendant symptoms reported in the present series included neither development of extrapyramidal symptoms nor any modification of existing extrapyramidal symptoms by the administration of CLN. The drug is distinct from the previously introduced antipsychotic drugs in this respect as well.

Hököfelt *et al.*¹⁴ described their experimental findings purporting to demon-

strate that CCK analogues constitute a part of the feedback inhibition mechanism for dopamine release in the lateral nucleus olfactory bulb region. In the present clinical investigation, effects on emotion and a psychoanaleptic effect were noted following administration of CLN in a relatively large proportion of the cases while no appreciable antihallucino-delusional effect or modification of extrapyramidal symptoms was noted, thus lending no positive support to its effect on the dopamine-neurone system. It would rather be of importance to take into consideration its possible influence upon other neural transmission systems such as the noradrenaline-neurone system and the 5-hydroxytryptamine-neurone system.

As for anorexigenic effect of CCK analogues, experimental data demonstrating their direct central action on the receptors of the hypothalamic ventromedial nucleus²⁶ and those evidencing indirect action affecting the transmission pathway from the peripheral receptor to the CNS via the vagus²⁷ have been reported. The existence of both central and peripheral receptors, therefore, is generally believed at present. Itoh et al.¹² have observed in their experimental study on stimulation of ACTH secretion in rats that both CCK-8 and CLN are devoid of direct effects on the CNS but act solely upon the peripheral receptor (in the abdominal cavity) for neural transmission to the CNS via the afferent vagal pathway in stimulating ACTH secretion from the pituitary. There does not exist any clear evidence to interpret the psychotropic effects of CLN observed in the present series as representing a direct central effect of the CCK decapeptide analogue. Thus, it cannot be simply ruled out that they were consequent on an indirect CNS action of the substance mediated by the peripheral receptor and afferent neuronal pathways, e.g. vagus. In addition, a major question of whether intramuscularly injected CLN can penetrate the blood-brain barrier without undergoing metabolic breakdown of its peptide structure is yet to be resolved. Further pursuit of study is considered urgently necessary in these respects.

CONCLUSION

It may almost safely be said from the present clinical trial that CLN exerts some psychotropic effects in a certain group of chronic schizophrenics. As yet, great many problems remain to be resolved, viz. necessity for clear characterization of these psychotropic effects, exploration of its effects in normal volunteers, effects of CCK-8, and so forth. Diverse clinical studies of the substance including double-blind controlled trials, therefore, are considered imperatively necessary upon strict confirmation of safety of CCK analogues, for its clinical application as a psychotropic agent rather than a diagnostic agent in internal medicine. Advances in basic research on the psychotropic effects of CCK analogues are

continually sought inasmuch as the site of their psychotropic action and the underlying mechanism are still entirely unknown.

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