RESULTS AND DISCUSSION

A. The relation between low tryptophan and low 5-hydroxytryptamine in the blood and the symptomatology of the patients

Aside from stupor, common features can be seen in the mental and muscular symptoms in the present patients. All four patients had very low concentrations of Try in blood, suggesting that low Try levels may have been responsible for their mental and muscular symptoms. In studies on carcinoid patients reported in the literature, chemical analyses have so far been restricted mainly to 5-HIAA, 5-HT and 5-HP. Only a few analyses of Try in blood have been reported in carcinoid patients, and they were found to be low (Sjoerdsema et al., 1956). No mental symptoms were mentioned in the patients, but in another report (Sjoerdsema et al., 1957) a carcinoid patient was described as occasionally frankly psychotic. Mental symptoms in other carcinoid patients have been reviewed by the author (Lehmann, 1972).

The first report in which a correlation between low Try levels in blood and mental symptoms was noted concerned patient C1 (Lehmann, 1966). The only analytical data in that report was 5-HIAA levels in urine. Later, data on levels of Try in serum and 5-HT in whole blood in patient C1 were published; serum Try was extremely low and 5-HT was high (Lehmann, 1972). In a subsequent report by the author, low levels of Try were described in association with a variety of mental symptoms in other carcinoid patients (Lehmann, 1972). Some of these patients were treated with Try for a short time, during which some of their symptoms were ameliorated. Unfortunately, further studies on these patients were not possible.

In regard to parkinsonian patients (P1 and P2), they also had low levels of Try in serum and low 5-HT levels in whole blood.
Both of these patients responded favorably to the Try treatment in the same way as was seen in the carcinoid patients, i.e. they woke up promptly from their stuporous states. There are, however, differences between the mental recovery in the carcinoid patients and in the parkinsonian patients. Normal mental behaviour returned in the carcinoid patients within one or two days of Try treatment, while improvement in parkinsonian patients occurred more slowly. Furthermore, parkinsonian patients failed to return to a normal mental state during Try treatment. These differences between effects of Try treatment on the mental condition in the two types of patients probably reflect differences in the biochemical basis of the diseases. In carcinoidosis, all enzymes necessary for the metabolism of Try can be assumed to be unaffected and the intestinal absorption of Try undisturbed. The low levels of Try seen in blood of carcinoid patients is presumably due to increased metabolism of Try in tumor cells. In Dopa-treated parkinsonian patients, on the other hand, low levels of Try in blood are due to malabsorption of Try from the intestine, as a result of competition between Dopa and Try for the common carrier (Lehmann, 1973). Degeneration of the intestinal mucosa in parkinsonian patients may also play a role in reduced Try absorption (Lehmann, 1973). It may be incorrect, however, to ascribe all the abnormalities seen in mental and muscular functions in Dopa-treated parkinsonian patients exclusively to malabsorption of Try, because Dopa inhibits absorption of other monocarboxylic acids as well (van Woert et al., 1970).

According to Munro (1970), Try is the first rate-limiting amino acid in protein synthesis, so a deficiency of Try can be expected to lead to diminished synthesis of protein. The increase in Try absorption and improvement in mental condition observed during Try treatment in patient P2 can presumably be explained by regeneration of cells in the intestinal mucosa (Munro & Goldberg, 1964) and increased 5-HT synthesis in brain. It seems therefore that at least two different mechanisms may be involved in disturbed metabolism of Try in patients with parkinsonism. One mechanism involves malabsorption of Try in the intestine leading to low levels of Try in blood and brain. The other concerns degeneration of enzymes responsible for the conversion of Try to 5-HT and of dopa to DA resulting in low 5-HT and DA in the brain.
The notion that 5-HT levels are suggested to be low in brain of parkinson patients is in agreement with findings of low 5-HIAA in CSF and in urine of dopa-treated patients (Guldberg et al., 1967; van Woert & Bowers, 1970; Johannson & Roos, 1971; Tyce & Muenter, 1970). Studies on laboratory animals also indicate that administration of dopa leads to a decrease in synthesis of 5-HT in brain (McGeer et al., 1963; Bartholini et al., 1968; Butcher & Engel, 1961; Everett & Borcharding, 1970). In the present patients, no direct evidence for low levels of 5-HT in brain was obtained as 5-HIAA in CSF was not analyzed. Be that as it may, the following discussion will assume that 5-HT levels in the patients were below normal. This assumption seems justified by several lines of evidence. In particular, low levels of 5-HT in brain can be assumed to have been present on the basis of the fact that Try levels in blood were extremely low and Try treatment alleviated stupor in all patients. Furthermore, in parkinsonian patients, 5-HT levels were low in blood and presumably also in tissues. It is therefore of interest to discuss the role of 5-HT in mental functions.

B. Comparison between the symptomatology of animals depleted of 5-hydroxytryptamine by para-chlorophenylalanine and the symptomatology of the patients

PCPA is a drug that selectively lowers 5-HT by inhibiting Try hydroxylase, the rate-limiting enzyme for synthesis of 5-HT. PCPA has been used experimentally to reduce 5-HT levels in both animals and man (Sicuteri, 1975). An account of behavioral changes observed in animals given PCPA as described by Weisman (1973) may provide guidelines for understanding the symptoms seen in the present patients.

The predominant change seen in PCPA-treated animals was a lowering of thresholds for both extero- and enteroceptive stimuli (Tenen, 1967). PCPA-treated animals tend to overreact to stimulation, although the changes in behavior may difficult to evaluate due partly to interactions between effects of PCPA on other monoamines and partly to the complexity of behavioral processes.
A lowering of 5-HT in brain seems, nevertheless, to be the main factor responsible for effects of PCPA on sensory thresholds.

a. Changes in sensitivity to exteroceptive stimuli: Skin and sense organs.

Hypersensitivity to tactile stimuli has been demonstrated in PCPA-treated animals given electric footshock or convulsant treatments. No observations have, so far as is known to the author, been reported on increased pain sensitivity in carcinoid or parkinson patients. Overreactions to visual, auditory, olfactory and gustatory stimuli were reported in PCPA-treated animals. For example, visual hallucinations were considered to occur in cats and monkeys given PCPA. One of the author's patients (P1) had olfactory hallucinations, and Mjölnäs (1949) noted visual and auditory hallucinations in parkinson patients not treated with L-dopa. That audiogenic hypersensitivity can be correlated to low 5-HT in brain is indicated by mice strains with genetically low brain 5-HT and supersensitivity to strong sounds which can cause death of the animals (Schlesinger et al., 1963; Kellogg, 1971).

b. Changes in sensitivity to interoceptive stimuli: Psychomotoric reactions, sleep, sexuality and mental behavior.

Abnormal psychomotor reactions such as aggressiveness, restlessness and convulsions were among the most pronounced effects of PCPA treatment in cats and rats. The symptoms seen in carcinoid and parkinson patients in the present study are also indicative of psychomotor reactions. One carcinoid patient (C1) had motor symptoms in the form of catatonic and cataleptic movements, restlessness and aggressivity. After having returned home, she became aggressive one day and beat her husband. Likewise, one of the present parkinson patients (P1) also became aggressive, jumped out of bed and hammered his hands against the wall. During the night he was often agitated and had to be treated with sedatives. Similar symptoms of aggressiveness and restlessness have also been described previously in parkinson patients (Calne, p. 91 1970) as well as in patients given PCPA (Engelman et al., 1967).

Of special interest is the sudden epileptic seizure that
occurred in patient P1 6 weeks after discontinuation of L-dopa. The patient had no history of epilepsy and the episode was therefore unexpected. Possibly the bilateral thalatomy performed one year earlier in this patient was a predisposing factor in connection with a low threshold for stimuli due to a decrease in 5-HT in blood (0.06 µg/ml) and presumably also in brain. Convulsant effects of PCPA have been demonstrated in animals and anticonvulsants have been shown to selectively increase 5-HT in brain.

Depletion of 5-HT is known to affect sleep (See several reports in Barchas & Usdin, 1973; Jouvet, 1967; 1968; Hartman et al., 1970; Hartman, 1977; Wyatt, 1970). In general, PCPA affects the sleep cycle by inducing insomnia with a decrease in slow wave sleep and paradoxical sleep (Jouvet, 1969). For example, in cats a decrease in 5-HT in brain leads to insomnia and a decrease in slow wave sleep. Restoration of sleep in PCPA-treated animals could be accomplished by administration of 5-HTP, while an increase of 5-HT induced hypersomnia.

Sleep disturbances are seen in several diseases. The high incidence of insomnia in L-dopa-treated parkinson patients (McDowell, 1970) indicates that insomnia is associated especially with this disease and can be expected to be correlated to the pathophysiology of the disease or its treatment. As L-dopa is precursor of noradrenaline and dopamine and these monoamines play a role in wakefulness, the insomnia of parkinson patients may be ascribed at least partly to L-dopa treatment.

Insomnia is not rare in patients with carcinoidosis. In patient C1 insomnia was an early symptom of disease. Hartman (1977) investigated the effect of L-Try in normal subjects and subjects with mild forms of insomnia and found that 1 g Try can reduce the sleep latency while a real increase in sleep time required doses of 5 - 10 g Try. Try has been used sporadically to treat insomnia especially in patients resistant to other remedies, but has not been found practical due to the expense and unpleasant taste of the treatment.

PCPA alters sexual behavior in animals (Koe & Weissman, 1966; Zitrin, 1973). PCPA treatment can, for instance, induce rabbits to mount male rabbits and also small dogs. Similar hypersexuality is also seen in PCPA-treated rats, and can be reversed.
by 5-HTP. Malmkja and Meyerson (1973) found a stimulatory effect of PCPA on copulatory behavior in castrated rats treated with submaximal doses of testosterone. Sodersten and Larsson (1976) found a similar effect of PCPA in castrated rats not treated with testosterone, an effect that could be counteracted by 5-HTP but not by L-dopa. The effect of PCPA is, however, inconsistent in so far as it varies with animal species.

Increased libido can occur in Parkinson patients treated with L-dopa (Calne, p. 87, 1970). In man, hypersexuality has been treated successfully with Try, while impotence has been improved by administration of PCPA (Sicuteri, 1975) or L-dopa (Benkert, 1970). In carcinoid patients, however, similar symptoms have not been reported and cannot be expected to occur due to their severe illness as also pointed out by Sjoerdema et al. (1970).

Mental disturbances produced by PCPA are best studied in humans. Cremata and Koe (1966) found PCPA to produce irritability, headache and malaise without behavioral aberrations in prisoners. It should, however, be noted that 5-HT levels were reduced only to half normal values by the PCPA treatment, which according to the author's experience is insufficient to induce mental symptoms. Of further interest are the observations of Engelman et al. (1967) and of Shani and Sheba (1970) on behavioral changes and mental symptoms in carcinoid patients treated with PCPA. The patients showed depression, anxiety, crying and agitation according to Carpenter (psychiatrist) who reviewed the mental disturbances in the PCPA-treated carcinoid patients of Sjoerdema et al. (1970). Several of the patients showed social withdrawal and lack of interest in their environment. No hallucinations or clearly delusional states were noted. Unfortunately, no analysis of Try or 5-HT was performed in the patients. However, judging from the clinical observations it is likely that the concentration of Try in blood before PCPA treatment may have been within the same low range as in patients described in the present report as well as in 6 carcinoid patients examined by Sjoerdema et al. (1967) in which a Try concentration of 0.45 - 0.8 mg/100 ml (21-39 µM/1) in serum was registered. As a result of low Try levels in blood, 5-HT in brain of these patients was probably also low. PCPA treatment in patients with low levels of Try and 5-HT presumably lowered the levels even further, thereby producing severe mental
symptoms.

With regard to the carcinoid patients described in the present report, C1 showed a series of symptoms characteristic of manic-depressive psychosis. After awakening from her comatose state she displayed symptoms of deep depression combined with catatonic muscular disorders. This condition was followed by confusion associated with hyperkinetic movements of her left leg and arm while she lay on her right side. She then became hypomanic and aggressive. It is noteworthy that these symptoms appeared in the same sequence when the Try treatment was repeated after a second period of stupor. The other patients with a tryptophan deficiency syndrome treated by the author showed depression, affective lability, excitation, hallucination, confusion, hypomania, motor disturbances, restlessness and stupor, at temporary unconscious at one time or another. The two parkinson patients resembled the carcinoid patients in so far as they had severe mental abberations including stuporous states. Furthermore, 5-HT in their blood was far below normal values and presumably was also abnormally low in brain. It is conceivable that some of the mental disorders observed in the present parkinson patients were a result of L-dopa treatment since adverse reactions to L-dopa including insomnia, delirium, confusion, hallucination, depression, restlessness, agitation, nightmares, paranoia, lethargy, stupor, psychosis, hypomania and hypersexuality are well known (See Goodwin, 1971; Calne, 1970; and Barbeau & McDowell, 1970 for reviews). It should be noted, however, that some of these symptoms also occur in parkinson patients not treated with L-dopa (Mjölnäs, 1940).

The foregoing discussion indicates that very similar symptoms are displayed under three conditions: 1) carcinoid patients treated with PCPA, 2) carcinoid patients not treated with PCPA by having nevertheless low serum Try and whole blood 5-HT levels, and 3) parkinson patients treated with L-dopa. The author considers the common factor for evoking symptoms in these patients to be low Try and presumably 5-HT levels in brain. This notion is supported by the observation that administration of Try lead to complete disappearance of symptoms in carcinoid patients and at least partial remission of symptoms in parkinson patients.
C. Time-related changes in behavior. Effect of meals

The effect of Try on behavior of patients was seen mainly in the morning during the first week after awakening from stupor. This was the case especially in patients P1 and C1. During the morning, these patients were in lively contact with personnel, spoke spontaneously and requested things to read or to drink for example. However, there activity declined around lunchtime and they usually became dull or stuporous for an hour or two after eating lunch. The regularity with which patient P1 became stuporous after lunch suggests that ingredients in the food eaten may have influenced the synthesis of 5-HT in brain - (Fernstrom & Wurtman, 1974). In that Try level in brain modulates the synthesis of 5-HT in brain (Fernstrom & Wurtman, 1971; Tagliamonte et al., 1973), it is likely that absorption of Try in the intestine and transport of Try into brain cells may have been diminished by constituents in the food. It is also of interest to note that patient P1 returned to his stuporous state every time he had an attack of pyelonephritis with high fever (Fig. 3). It is probable that brain 5-HT level was decreased in P1 due to increased neuronal metabolism during the fever (Corrodi et al., 1967).

The general impression of patient P1 was that his brain functioned like a poorly loaded battery, which was charged-up during the night with 5-HT after administration of Try in the evening and discharged during the morning due to neuronal activity. The administration of Try in the evening has the advantage of increasing sleep (Hartman, 1977). The diurnal changes and day-to-day variations in mental behavior of P1 reminds of the "on-off" phenomenon in muscular symptoms in parkinsonism.

The notion that constituents in food may influence Try metabolism in brain is supported by many recent studies (Fernstrom & Wurtman, 1972; 1974; Perez-Cruet, 1974; Fernstrom, 1979; Hartman & Wurtman, 1977). In particular, amino acids compete with Try for transport by a common carrier in cell membranes. Short-branched amino acids such as valine, leucine and isoleucine inhibit Try transport so the ratio between Try and the sum of these amino acids may be a determining factor for Try transport (Perez-Cruet et al., 1974; Fernstrom, 1979). This ratio may also be of importance for the therapeutic effects of Try in affective...
disorders (Müller et al., 1976). In some patients, large doses of Try may be required in order to overcome competition with other amino acids. For example, little improvement in the condition of patient P2 was noted in the present study when 1 g Try was given 3 times daily together with meals, but a remarkable improvement was noted when 3 g Try was given in a single dose in the evening, 3 hours after dinner. Evidently, Try therapy in stuporous patients, as well as L-dopa therapy of parkinsonism (Cotzias, 1968) may be less effective when administered in connection with meals.

The influence of meals on the mental condition of the present patients may reflect their enhanced sensitivity to dietary components. Patients with low levels of Try in serum and 5-HT in whole blood may be more sensitive than normal subjects to factors influencing the synthesis of 5-HT in brain. It is interesting to note that Perez-Cruet et al. used patients with parkinsonism, Huntington's chorea and other neurological diseases to study dietary effects of Try. Patients with these diseases may be particularly sensitive to factors influencing Try metabolism. In addition, different degrees of Try malabsorption have been observed in parkinson patients (Lehmann, 1973). It is tempting to speculate that the mental condition of patients with certain diseases may be more sensitive than that of normal subjects to the influence of food, in part due to abnormalities in Try and 5-HT levels.

D. The effect of raw tissues on the symptomatology

The present findings show raw meat and other raw tissues to have beneficial effects on mental disturbances in patients with carcinoidosis or dopa-treated parkinsonism. It seems worthwhile to follow-up this observations in the treatment of similar patients. If the beneficial effect can be found in other patients suffering from similar disorders, a factor other than Try also may be of importance for mental behavior in the patients, as the content of Try in the tissues (ca. 0.6 g L-Try/300 g ox meat) is too low to be responsible for the effect. In this regard, it is to be noted that Ljungberg (1963 and personal communication) used raw tissue (liver, kidney and thymus) in the treatment of stuporous schizophrenic patients who had catatonia.
and high excretion of 5-HIAA. The administration of raw tissues was combined with intensive insulin-coma therapy and prochlorperazine. According to Ljungberg, most of his patients "became rational" during the treatment. Whether the beneficial effects were due primarily to factors in the raw tissues, effects of insulin or of the drug is unknown. The findings are nevertheless of interest with respect to the present observations on beneficial effects of raw tissues in stuporous patients (Fig. 3).

E. The tryptophan deficiency syndrome. Analysis of the muscular and mental symptoms

The combination of muscular and mental symptoms seen in the present patients is of special interest as it has motivated the author to consider the symptomatology to represent a special syndrome. This notion was based on the finding that a deficiency in Try and 5-HT was associated closely with the symptoms and that Try therapy was able to alleviate the symptoms. In the following, the role of 5-HT mechanisms in the muscular and mental symptoms described in the patients will be analyzed further.

Analysis of the muscular symptoms

As there are serotoninergic neurons in the spinal cord (Dahlström & Fuxe, 1965; Fuxe, 1965) they may have been activated during the Try infusions, which presumably lead to the availability of more free Try than in normal blood. Presumably Try has induced sufficient synthesis of 5-HT for awakening the patients and for stimulating the spinal 5-HT pathways. There are, however, differences of opinion about the motor effect of 5-HT in the CNS (See minireview of Gerson & Baldessarini, 1980). According to Gerson & Baldessarini an increase in brain 5-HT in rodents produced by 5-HT precursors or by infusion of 5-HT in the CNS has an inhibitory effect on motility whereas a decrease in 5-HT after brain lesions or treatment with PCPA or Try-free diets produces hyperactivity. For references see Gerson & Baldessarini. In addition, certain hyperserotoninergic conditions are also associated with hyperactivity, the so-called "serotonin syndrome". This syndrome is seen in rats and other animals treated with 5-HT precursors after
treatment with drugs facilitating 5-HT synthesis as, for example, MAO and decarboxylase inhibitors. Thus, either hyposerotoninergic and hyperserotoninergic conditions have been found to have excitatory effects on movement in experimental animals. However, there are also experiments in which the above mentioned drugs have not been used and hyperactivity nevertheless has been observed after treatment with 5-HT precursors given either systemically or locally in the CNS (intraventricular injection) or in the spinal cord. Similar effects have been obtained by electrical stimulation of the raphe-spinal 5-HT pathways. All these experiments are, however, uncertain as in some experiments no effect has been seen, and in others suppressant and/or excitatory effects on motoneurons have been observed. For review see Barasi & Roberts 1974. It is also unclear whether stimulation influences the motoneurons directly or indirectly via an interneuron as suggested by Grillner & Uno (1970). It has been suggested that the effect on both locally applied 5-HT as well as electrically-stimulated raphe pathway can increase lumbar motoneuron excitability via release of 5-HT in the ventral horn of the spinal cord (Barasi & Roberts, 1974). Furthermore, it has been proposed that the descending projections to the spinal tract are excitatory whereas ascending projections to the forebrain are inhibitory on spontaneous muscular behavior (Gerson & Baldessarini, 1980).

It should be noted that in all these experiments in which excitatory effects have been elicited in combination with hyperserotoninergic conditions, the animals have been either treated with drugs or operated; none were intact and physiologically normal. It is evident that despite previous experimental work on the motor effect of 5-HT, there is still great uncertainty on the role of 5-HT on motor behavior of animals, so the use of findings obtained in animals is only of very limited or no value as a guide for understanding the clinical symptomatology seen in the present patients.

The muscular symptoms seen in the present patients were most pronounced in C1 and P1 during intravenous infusion of Try after awakening from stupor. It is, however, uncertain whether normal or possibly supernormal levels of 5-HT were obtained in these patients. Before Try-infusion, it can be suggested that brain 5-HT levels were extremely low during stupor as indicated by the low
levels of Try and 5-HT in blood. Furthermore, it can be noted that the epileptic seizure in patient P₁ before treatment with Try suggests a hyposerotoninergic conditions, as convulsions are frequently seen in animals treated with PCPA (Koe & Weissman, 1966) or deprived of 5-HT by a Try-deficient diet (Boulin, 1965). Likewise, spastic muscular symptoms were seen in the legs of an elderly, stuporous patient with low Try levels before Try treatment (not reported here in detail. See p. 48). It seems thus reasonable to consider these symptoms to be of hyposerotoninergic origin.

It would have been of interest to have determined 5-HIAA in the CSF of the patients before treatment with Try, as low levels suggest that the level of 5-HT in brain is low. (Ashcroft & Sharman, 1960). For the evaluation of a possible hyperserotoninergic condition during infusion of Try the analysis of CSF 5-HIAA levels would have been of no value, however, because of the delay for the cisternal fluid to reach the lumbar tract (8 hours) and for 5-HIAA to diffuse from the brain cells to the cisterns (unknown). During this time, the muscular symptoms changed so no close temporal relation between 5-HIAA levels and muscular behavior would have been found. This time-delay excludes the possibility of diagnosing a possible normal or hyperserotoninergic condition during muscular hyperactivity be means of 5-HIAA levels in the CSF. It may, nevertheless, be possible to approach a differential diagnosis between a hyperserotoninergic and a hyposerotoninergic condition in relation to motor disturbances. If a hyperserotoninergic conditions had been present, then it could be expected that 5-HT had accumulated in the storage granules in the synaptesomes and neuron bodies respectively - small and large compartments according to Garfinkel, (1966). Likewise, Try could accumulate by binding to albumin (See Grahame-Smith, 1973, for further discussion). The present findings speak against the involvement of such "pools", however, in that the patients returned to their stuporous states as soon as the infusions of Try were stopped. Had "pools" been involved, they would have been expected to delay the return to stupor. It should furthermore be noted that 5-HT levels in brain were - as mentioned - most probably low when the infusion was started and that 98 per cent of Try is transformed to other metabolites than 5-HT, which leaves only 0.1 g 5-HT from the 5 g of Try infused. The author is therefore of the opinion that the muscular activity
seen during Try infusion was due to a hyposerotoninergic condition and that the symptoms thus resemble those seen in 5-HT-deficient animals.

It is also of interest to discuss findings on the character of muscular symptoms in humans in which abnormalities in 5-HT have been reported. Coleman (1971) has analysed 5-HT in hyperactive children and found it to be low in 88 per cent of them, although none of them showed evidence of neurologic dysfunction. Upon hospitalization, the level of 5-HT in the children rose and their hyperactivity lessened. After discharge, the level of 5-HT in the children decreased and their symptoms of hyperactivity reappeared. Greenberg & Coleman (1976) determined total hydroxyindoles, HI, in 24 mentally retarded hyperactive patients and found low levels in 83 per cent of them. After treatment with psychoactive drugs, HI rose to normal levels and the hyperkinetic syndrome disappeared in most of the patients. However, in those patients who remained hyperactive during drug treatment, HI levels continued to be low. These findings indicate that hyposerotoninergic conditions are associated with hyperactivity in man.

Hyperserotoninergic conditions, on the other hand, are rare. Large doses of Try induce sleep (Hartman, 1970) and in hepatic coma, high concentrations of Try and 5-HT are found in brain (Knell et al., 1974; Job et al., 1966; Munro et al., 1975), so there is some evidence that suggests high concentrations of 5-HT to "facilitate" the occurrence of coma (Munro et al., 1975). However, a clear-cut connection between hyperkinesia and hyperserotoninergic condition in humans has not, as far as is known to the author, been demonstrated.

Analysis of mental symptoms

Stupor and coma are the mental symptoms of utmost interest for the present report, and it is tempting to speculate on how these conditions may have been induced in the patients. If a 5-HT pathway directly or indirectly activates brain regions which maintain consciousness, and if impulse activity in this pathway gives insufficient transmitter release to evoke an action potential, then the results will be a decreasing degree of consciousness and eventually stupor or coma. With regard to this notion, it is of
interest to review effects of low 5-HT levels on states of consciousness in experimental animals.

In animals in which 5-HT had been decreased by PCPA (Koe & Weissman, 1972), no signs of lethargy were seen but it is doubtful that the treatment inhibited the synthesis of 5-HT sufficiently. On the other hand, signs of reduced awareness have been observed in rodents given Try-deficient or Try-free diets (Boullin, 1975; Fernstrom & Wurtman, 1972; Perez-Cruet et al., 1975). In particular, animals with no 5-HT in brain after a few weeks of Try-free diet became lethargic and showed ataxia, muscular rigidity and spasms (Boullin, 1965), behaviors similar to those seen in some of the present patients, especially C1. Thus, severe deficit in 5-HT may be associated with lethargic states and mental symptoms. It is therefore reasonable to suggest that stupor and coma in the present patients reflected a severe hyposerotoninergic condition. A co-operation of other Try metabolites, insufficient protein synthesis or polypeptides cannot be excluded but is difficult to demonstrate.