Psychiatric and Neurological Reactions to Cycloserine in the Treatment of Tuberculosis*

WILLIAM C. LEWIS, M.D., GEORGE CALDEN, PH.D.,
JOHN R. THURSTON, PH.D. and WARREN E. GILSON, M.D.
Madison, Wisconsin

Early observations on the use of cycloserine have revealed disturbing emotional and neurological side effects attendant upon the administration of this new antibiotic to a number of patients with pulmonary tuberculosis.\(^1\) \(^2\) \(^3\) Perhaps the most striking of these reactions have been epileptiform seizures, varying from slight tremors to grand mal convulsions. In most of these cases, the convulsions occurred among patients who had no previous history of epilepsy. Several patients also were reported to have experienced marked changes in mood ranging from depression and somnolence to excitatory reactions.

The aim of this study was to evaluate further the psychiatric and neurologic reactions of patients to cycloserine. This investigation is part of a broader pilot study on cycloserine therapy being conducted in Veterans Administration hospitals in conjunction with the Veterans Administration-Armed Forces Study on the Chemotherapy of Tuberculosis.

**Materials and Methods**

Thirty men initially were selected for inclusion in the cycloserine therapy program. The criteria for selection of these subjects consisted, in each case, of the presence of a positive sputum smear, the absence of any evidence of epilepsy, renal or hepatic disease, dermatitis, or allergy. The age range of the group was from 29 to 70 years (mean age, 46 years). One of the subjects was an American Indian, five were Negroes and the remainder were white. Twenty-three were diagnosed as having far advanced pulmonary tuberculosis and seven had moderately advanced disease. Fourteen of the 30 were original treatment cases without previous chemotherapy. The remainder were retreatment cases. At the start of the study, all of the patients received 0.5 gm. of cycloserine twice each day.

Within a few days after presentation to the medical therapy board and before cycloserine was begun, each patient was seen by the investigators in order to obtain electroencephalographic tracings for the waking and sleeping state and a clinical evaluation of the mental and neurological status. Psychological tests were employed to assess the patient's mood and mental capacity, his adjustment to hospitalization and his attitudes toward cycloserine.

---

*From the Psychosomatic Department of the Medical and Tuberculosis Service, Veterans Administration Hospital.
In addition to the initial pre-drug evaluation, patients were interviewed by the hospital's consulting psychiatrist and given psychological tests one month and then four months after the first administration of cycloserine. Routine electroencephalographic tracings were obtained one week after the initiation of the drug and at monthly intervals thereafter. Additional interviews were requested when any marked signs of abnormality were noted by the ward physician.

RESULTS

Electroencephalographic Studies

The number of electroencephalograms obtained from the 30 subjects varied from one to eight, with an average of five administrations per patient. Of the four subjects who had less than three tracings, two (re-treatment cases) died shortly after the start of the study. A third was taken off cycloserine because of severe depressive symptoms attendant upon the initiation of chemotherapy. Cycloserine also was discontinued with the fourth patient because of the occurrence of spontaneous pneumothorax. The latter two were original treatment cases.

Prior to initiation of cycloserine, the tracings of all patients in the study were essentially normal. With the exception of one (S.R.) all tracings remained consistently normal and showed no significant changes during the subsequent four-month periods of chemotherapy. This one patient, a 36 year old, white man, with far advanced disease, and a re-treatment case, experienced a grand mal seizure during the ninth day after he was placed on the drug regimen. The blood level on the seventh day was 42 mcg/ml. As a consequence of his grand mal attack, he was immediately taken off cycloserine. His electroencephalograms clearly reflected this episode. One week before he was placed on cycloserine, his tracings had been within normal limits and had revealed a basic rhythm of 9-10/second 10-30 microvolt waves, low voltage fast and droway activity. One week after his seizure, his electroencephalographic record showed definitely abnormal trends involving short runs of generalized 2-3/second 40-200 microvolt waves. His basic rhythm consisted of 8-10/second 10-20 microvolt waves and low voltage fast activity in normal distribution. A follow-up set of tracings, nine days later revealed an even more abnormal record involving almost continuous generalized 2-3/second 50-250 microvolt waves. The basic rhythm consisted of 9-10/second microvolt waves, and low voltage fast activity in all leads. An additional set of tracings were made three weeks later (i.e., five weeks after the discontinuance of cycloserine). The abnormal findings at this time were no longer in evidence and the tracings again were within normal limits indicating the disappearance of residuals of his grand mal seizure.

A second patient (M.E.) also experienced a grand mal bilateral seizure two weeks after the initiation of cycloserine. As a result he was taken off the drug. However, no significant change was observed in his essentially normal electroencephalograms. (A more detailed discussion of this patient is presented below as case 5 in the psychiatric section).
A third patient (D.A.), was a 35 year old Negro who had been ill for six years. He had had numerous hospitalizations, chemotherapy, and peritonitis, but in spite of these measures his disease progressed and chronic cirrhosis with right ventricular failure eventually developed. Secondary to this he had liver congestion with many abdominal complaints. After digitalization there was some relief. He was placed on cycloserine but within seven days he became quite somnolent and on the 10th day had a grand mal convulsion. His cycloserine blood level for the third, fifth and seventh days was 62.5, 50, and 54.5 mcg/ml. On the 11th day cycloserine was discontinued. On the 22nd day he developed acute toxic delirium with paranoid ideas and threatening behavior which cleared rapidly. Malnutrition, far advanced disease and chronic anoxemia due to right heart failure were considered to be important factors. Electroencephalographic examination was not available because of his critical condition, but the neurological examination was unchanged from his pre-treatment examination. His course was progressively downhill with increasing heart failure and death a month later.

Thus, in the 26 patients studied, three suffered convulsive seizures which probably were related to cycloserine. However, in only one did changes from normal to abnormal occur in electroencephalograms. The effect of cycloserine on the EEG records of the majority of patients was negligible.

Psychiatric Studies

The initial psychiatric interviews with the 30 patients lasted approximately 45-60 minutes. A brief life history was obtained and an attempt was made to exclude from the study all showing borderline psychoses, previous psychotic episodes, severe character disorders, evidence of organic central nervous system disease, and severe neuroses. A number of candidates for the study were on this account excluded. However, no attempt was made to obtain a "normal" sample. Rather, an effort was made to exclude only those in whom a recurrence of a previously existing emotional or neurological disease would be likely to occur on a spontaneous basis, which would be apt to be confused with the psychiatric manifestation of cycloserine toxicity. The indices for inclusion into the sample are thus

\[
\text{TABLE I}
\]

<table>
<thead>
<tr>
<th></th>
<th>Blood levels in mcg./ml.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Number of toxic patients</td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>2</td>
</tr>
<tr>
<td>Grade II</td>
<td>1</td>
</tr>
<tr>
<td>Grade III</td>
<td>0</td>
</tr>
<tr>
<td>Number of asymptomatic patients</td>
<td>1</td>
</tr>
</tbody>
</table>
obviously quite crude. Owing to the nature of the patient population, a
number of deviant personalities were included, some of whom were con-
sidered merely eccentric in character structure, and others who had shown
poor occupational and social adjustment, but displayed no outright psy-
chosis. A number of subjects had a history of alcoholism in the past.

After the more detailed initial examination, patients were seen at the
intervals described, usually for a much briefer period. In actual practice,
one of the investigators would drop in for a brief chat in the patient's
room and ask him routinely about subjective symptoms. In the absence
of any complaint on the part of the patient a neurological examination
was usually done and a consultation held with the ward nurse. In the
presence of complaints, a more detailed inquiry was made and a more
exacting neurological examination performed. In some instances, follow-
up interviews would last as long as the initial one. But in most cases
the contacts with the patient were more in the nature of a screening
interview. The patients all knew that they were receiving a new drug,
and, as in all such cases, rumors circulated amongst the patients with
great rapidity. It was thus impossible to exclude the factor of sugges-
tion, contagious fear and suspicion, or on the other hand, unwarranted
optimism and blunting of subjective observations of pathological symptoms.

It was also impossible to isolate these patients either from the usual
conflicts which occur within a patient population, both between patients
and with the staff, or from the usual problems arising from extra-hospital
sources (family problems, marital difficulties, etc.). The patients were
also aware of changes in their disease from time to time and their esti-
mates of their subjective state was bound to be influenced by periodic
orientations given to them by ward physicians. Thus the psychiatric
evaluations cannot claim to be in any sense controlled, quantitative and
precise, but are presented here with all the reservations imposed by the
nature of the study.

Of the 30 patients, 15 showed some degree of change referrable to the
neurological or psychiatric sphere. On the basis of previous studies, in-
vestigators had been alerted to look for and ask the patient about a number
of specific symptoms. These included (in ascending order of severity),
drowsiness, somnolence, mood changes, hyperactivity, personality changes,
psychotic episodes, and convulsions. In the 15 patients mentioned, certain
additional symptoms also were observed. Assuming for the moment that
there is a pattern typical of cycloserine intoxication, patients thus affected
may exhibit the following signs and symptoms, graded for analytic pur-
poses into three syndromes of increasing severity:

Grade I: Shortly after the beginning of cycloserine treatment (from a
week to a month), the ward personnel notice that the patient is hyper-
irritable, snappish and is making some puzzling and inappropriate re-
marks in a fashion different from his usual behavior. When seen by the
psychiatric interviewer, the patient complains of slight drowsiness, ir-
ritability, some muscle twitching, slight dizziness, but shows otherwise
essentially normal behavior.
Grade II: In addition to the above, some patients evidence marked mood swings, hostility and irritability, depression, unreasonableness toward personnel routines and other patients, withdrawal and suspiciousness and threats of irregular discharge.

Grade III: In several instances there resulted pronounced personality and mood changes to the point of either borderline psychosis or increasing confusion culminating in a full-blown psychosis. Included in the Grade III disturbances are cases showing some of the less severe psychiatric symptoms, but also evidencing much greater neurological hyperirritability culminating in grand mal convulsion.

Of the 15 showing some type of change, five presented only the mildest group of symptoms (Grade I level). Four showed Grade II symptoms and six had Grade III level disturbances. Examples of each type will be briefly presented below. In all cases, save one, there was a return within a period of 10 days to the pretreatment status following withdrawal of the drug.

### TABLE II

COMPARISON OF BLOOD CYCLOSERINE LEVELS DURING PERIOD OF TOXIC SYMPTOMS WITH AVERAGE DURING ASYMPTOMATIC PERIODS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Blood levels in mcg./ml.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Toxic period</td>
</tr>
<tr>
<td>Grade I</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>13 - 19</td>
</tr>
<tr>
<td>3</td>
<td>22 - 29</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>20 - 24</td>
</tr>
<tr>
<td>Grade II</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>13 - 16</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Grade III</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>11</td>
<td>54</td>
</tr>
<tr>
<td>12</td>
<td>32 - 39</td>
</tr>
<tr>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>14</td>
<td>41</td>
</tr>
<tr>
<td>15</td>
<td>17 - 48</td>
</tr>
</tbody>
</table>

*These patients were immediately toxic after drug administration began.
Vol. XXXII
NP REACTIONS TO CYCLOSERINE 177

Case 1 (Grade I): This is a 39 year old single white man who had been seen in psychiatric consultation before the beginning of the study because of some periods of withdrawal, suspiciousness and hostility, with mild emotional outburst. He was diagnosed as having a mild schizoid personality, was suffering from reactive depression due to prolonged hospitalization and the downhill course of his disease. Usually after a period of discussion with a ward physician his episodes of depression disappeared. He was accepted for the study and at the beginning of the drug administration was in a period of relatively good adjustment. Within the first two weeks (questioned directly) experienced muscle twitches in the forearm and shoulders occurring irregularly and transiently, not involving movements of the whole arm. He denied mood changes, irritability, somnolence or neurological symptoms. The follow-up neurological examinations and succeeding interviews at the later examination periods were all within the normal limits to the end of the period of the study. Blood cycloserine levels ranged between 22 and 37 mcg./ml and were in the neighborhood of 30 mcg./ml during the period of symptoms.

Case 2 (Grade I): A 45 year old white man had been in this and other hospitals intermittently for approximately five years, with increasing severity of his disease, despite treatment. He is considered to be a man of stable occupational and social adjustment with good family relationships and a generally optimistic temperament, who withstood the ravages of disease with great fortitude. He was considered to have essentially normal personality and to be free of psychiatric illness. One month after the drug was begun, he stated that he felt an occasional muscle twitch in the arm and shoulder muscles and that he was perhaps slightly more irritable than usual but that he had no further difficulty. Interview with the ward personnel confirmed that he was his usual self.

In an interview approximately three months after the beginning of administration of the drug, he stated that he had experienced muscle twitching, slight somnolence and headache, and that he was rather dizzy and irritable. The night before he was seen he had been sitting at the dining room table. He had a sudden panic experience in which he felt that he was going to "fly into many pieces." He was partially disoriented, said that he could not focus, and experienced a twitching of the left arm, neck and right arm. He returned to his bed and within a few minutes was feeling all right. There was no loss of consciousness but he did feel confused, light headed and "not himself." There was no recurrence of this experience. Neurological examination the next day was entirely within normal limits and his mental status was not different from that noted on previous contacts. He had been a rather easy-going, well integrated person, so the likelihood of a hysterical or near-schizophrenic panic, or of a phobic attack seems small. Because of the concomitant twitchings it was considered that probably he had experienced a transient toxic reaction to the drug. Blood cycloserine levels had been in the neighborhood of 40 mcg./ml for the first few weeks of treatment, but on the 90th day was only 19 mcg./ml. There was no recurrence of these episodes. Past history reveals no similar episodes in this man's life.

Case 3 (Grade II): This 33 year old white man had tuberculosis for many years and had been exposed to nearly all the drugs without appreciable improvement. In a previous hospitalization he had been considered to be sufficiently deviant in personality and to be showing enough symptoms to warrant a psychological and psychiatric investigation. Psychological tests indicated a rather severe schizoid personality with indications of a threatened schizophrenic decompensation. Observed in this hospital from time to time by the psychiatric staff, he appeared to have an obsessive-compulsive personality with certain schizoid features. However, no definite psychotic symptom was observed. Adjustment to this hospital was stable with the exception of one or two temper outbursts at frustrations within the hospital. As the neurological examination was normal, he was included in the study. He experienced a mild depression prior to going on the drug because he had hoped to go home for some treatment. He decided to remain and take cycloserine. For approximately five weeks he experienced no difficulty with the exception of slight increase of sleepiness and "wooziness." Seen on routine evaluation, there was no change from his general mental status as observed before. Two weeks later, however, he was seen after having been on a five day pass. For approximately 10 days before this examination he said he had been extremely tense and had the feeling he was having marked twitching movements of his extremities. When lying flat in bed, for example, he would have the impression that his arm had suddenly twitched and flopped across his chest but when he woke up he couldn't actually verify whether this had occurred or not. He had been feeling dull mentally and had been having headaches, was dizzy and depressed. At this time blood cycloserine levels had been in the neighborhood of 15 mcg./ml for several weeks. This man had been placed on 1 gm. cycloserine b.i.d. for 10 days, 0.75 gm. b.i.d. for 25 days, and 0.5 gm. b.i.d. for another 38 days with only mild recurrence of twitching and instability.
Case 4 (Grade III): This 57 year old white, married man had known tuberculosis for three years though probably ill much longer. He denied having had neurotic or neurological symptoms and had never been hospitalized for mental illness. He claimed to be of an even, easygoing temperament. The past history indicated that he had only finished the seventh grade in school, had been a laborer of various sorts most of his life, and had been running a bait business most recently. He gave a history of rather heavy drinking over a period of years, but denied any ill effects and claimed to have been moderate in recent years. Examination of mental status revealed an extremely garrulous and circumstantial manner of speech without any incoherence or irrelevancy. He had some rather primitive ideas of the patent-medicine variety. His ward behavior was in the realm of normal. The neurological examination was normal. He was considered to be somewhat eccentric and hypomanic but not sufficiently disturbed to be ruled out from the study.

After 16 days on cycloserine, he was seen again at the request of the ward physician. His blood cycloserine level was 39 mcg./ml. on the 14th day. He wrote rambling and confused letters. He was fleetingly aware that he might be suffering delirium but this was transient. His wife had visited him and noticed an obvious change and felt that he was seriously disturbed. The neurological examination was unchanged. He was considered to be suffering a toxic psychosis of a manic variety with some schizophrenic undertones. The drug was stopped and he was placed on special observation. During the next several weeks his mental status improved and he appeared to have returned to normal at times. However, occasionally, confused episodes persisted. He eventually was transferred to a neuropsychiatric hospital. He subsequently returned to this hospital some six months after the psychotic episode. He has apparently returned to his former somewhat eccentric personality adjustment without evidence of psychosis at the present time.

Case 5 (Grade III): This 55 year old white man has been ill for only two months. The initial screening examination did not reveal evidence of neurological or psychiatric disorder. Two days after he was placed on cycloserine he began to complain of dizzy spells and tremor. The blood cycloserine level was mcg./ml. He appeared to the nurses to be euphoric and hyperactive. Ten days later he began to experience blackout spells a few seconds at a time. A ward physician examined him and found hyperactive deep reflexes. An electroencephalogram at this time was considered normal. He was taken off the drug but three days later suffered a grand mal seizure and there was persistence of the former symptoms of dizzy spells, tremor, hyperactive reflexes and blackout spells. These gradually disappeared in the succeeding three weeks.

The above cases are presented for purposes of illustration. Patients in the Grade I and II groups had difficulties which lent themselves to rather clearcut and consistent classification. The patients grouped in the Grade III classification had more heterogeneous and less consistent disturbances. There were two other patients who had a grand mal seizure. In one case, this was not accompanied by any marked psychiatric symptoms and the patient returned to normal within a few weeks. In another case there was a toxic delirium. Four patients other than those reported above have had marked changes (Grade III) in personality together with some indications of neurological disturbance. These patients presented syndromes which involved intricate mixtures of responses to marked external stresses, responses to marked interpersonal difficulties in the hospital, preexistent character difficulties and acute exacerbations of personality maladjustment. In one grade III patient, terminal toxicity from devastating tuberculosis was probably a factor in producing a convulsion and toxic delirium.

The relationship of toxic symptoms and signs to blood cycloserine levels remains obscure (Table I). Our studies fail to disclose a significant difference in average blood levels between those patients showing toxic symptoms and those who had no symptoms. The number of cases is too small to permit conclusions covering the higher levels found in three patients.
showing grade III disturbances. One of these was almost moribund from congestive failure. The levels found at the time symptoms were being experienced by patients who showed toxicity were not different from the average blood levels in these patients (Table II).

**Psychological Tests**

The following psychological tests were used: the Guilford Inventory of Factors STDCR, the Madison Sentence Completion Form, the Madison Irregular Discharge Scale, the Ward Behavior Scale and the Benton Visual Retention Test.

The Guilford Inventory (4), a "yes-no" type of personality questionnaire was chosen for the study in order to evaluate the extent to which the drug might make the patient either more cheerful or depressed, extroverted or intraverted, happy-go-lucky or serious minded, flighty or stable. The Madison Sentence Completion Form (5) is designed to evaluate the attitudes and emotional reactions of tuberculous patients. Five incomplete sentences were added to the form in order to elicit the patient's specific attitudes to the drug itself as well as his feelings about being on cycloserine therapy. The five sentence stems are:

1. When a patient is first told he will get the new drug . . .
2. The new drug I am getting . . .
3. Ever since I have been taking the new drug . . .
4. Taking the new drug makes me . . .
5. The chances of my getting better . . .

In addition to its value as an indicator of irregular discharge potential, the Madison Irregular Discharge Scale (6) was employed in this study as a means of appraising the effects of the drug upon the patient's general ability to adjust to hospitalization. The Ward Behavior Scale (7) is a measure of the patient's daily conduct on the ward as seen through the eyes of the ward nurse. The scale enables the nurse to rate the degree to which a patient "misbehaves," i.e., to what extent does he disregard hospital rules, violate his bed rest classification and indulge in objectionable social behavior with fellow patients and staff personnel. The Benton Visual Retention Test (8), a test in which the patient reproduces geometric designs from memory was used to investigate the possibility that cycloserine therapy may induce the impairment of mental functioning as a consequence of organic brain disturbance.

Eighteen of the original 30 subjects were given the complete psychological test battery and were tested the required three times (once before, and twice after the initiation of cycloserine). It was not possible to obtain complete test results from the other 12 patients. This was due to the discontinuation of cycloserine treatment because of death, undesirable side effects or premature discharge from the hospital against medical advice. Two of the 12 patients who continued in the study refused to submit to all the testing. It must be made clear that the remarks below pertain to those patients who did not show marked (grade II or grade III) signs of toxicity, and therefore relate to the effects of the drug upon more "average"
or "normal" patients.

The Guilford Inventory test-retest results did not reveal striking changes in mood attendant upon the administration of cycloserine. The difference in mean scores for each of the five factors of mood and emotionality showed only slight alteration of affect during the three testing periods. None of the differences in mean test-retest scores assumed statistical significance (at the 0.05 level of confidence).

The scores on the Benton Visual Retention Test also showed no significant test-retest changes. These results suggest that in the absence of acute toxic effects, cycloserine had no durable effect on the patients' memory functioning, capacity for being attentive or visual-motor coordination.

With the exception of those patients showing grade II and III disturbances, the ratings of the patients' ward behavior before and during cycloserine therapy were substantially unchanged. Similarly, their overall capacity for adjusting to hospitalization, as reflected in their scores on the Madison Irregular Discharge Scale, underwent minimal changes during the four-month testing period. On the other hand, those patients in the grade II and III categories showed a trend toward worsening of hospital behavior.

In general, when patients were first informed that they were selected for treatment they accepted the news rationally and hopefully. There was no joyous "dancing in the aisles" comparable to the euphoric reactions allegedly associated with the initial administration of isoniazid. Instead, the predominant reaction of the patients as indicated in their responses to the Madison Sentence Completion Form was "Let's try it out."

Before the start of treatment, the 18 subjects who completed the battery of psychological tests, expressed diverse feelings about their chances of recovery as a consequence of getting the drug. About one-third of them felt optimistic; another third qualified their optimism by expressing hope that the drug would work out well, and the remaining third seemed to adopt a "wait and see" attitude.

A reassessment of attitudes both one month and four months after the inception of therapy indicated that their feelings about recovery did not undergo uniform changes. After three months of treatment, four patients retained their original attitudes, eight felt more optimistic about recovery and six felt less optimistic.

The subjective reactions to cycloserine varied considerably from patient to patient after one month of treatment and after four months of chemotherapy. After four months, six of the 18 patients stated that they had "felt a lot better" as a result of the drug. Eight indicated that there had been no change in their reactions; and five complained of adverse side effects; "It's made me more nervous." "Several times I got so dizzy I practically blacked out." "I've had that dull, broken-down feeling ever since I began taking the medicine."

In general, the psychological tests do not reveal any uniformly significant trend in alteration of mood, mental status, hospital adjustment or attitudes toward cycloserine therapy.
SUMMARY

Of 30 patients placed on cycloserine, half showed some type of psychiatric or neurologic change of varying severity. Six showed severe disturbance of function, either manifested by mounting signs of central nervous system instability culminating in grand mal convulsion (three patients) or in borderline or outright psychoses (three patients). Psychological test results of the "normal" group (i.e., those not showing obvious psychiatric symptoms) did not show significant alterations in mood and attitude during the course of treatment. Repeated EEG’s were normal except in only one case despite the occurrence of seizures in three. Some of the difficulties involved in assessing the role of cycloserine in the causation of these changes are described, and typical cases are presented together with data regarding blood cycloserine levels. In any future attempt to evaluate cycloserine toxicity it appears to be essential to obtain as normal a sample of cases as possible, and pending such studies, cycloserine treatment of psychiatrically disturbed persons should be undertaken with considerable caution.

RESUMEN

Entre 30 enfermos tratados con Cicloserina, la mitad mostraron algún cambio psiquiátrico o neurológico de severidad variable. Seis mostraron cambios graves de función manifestándose ya sea signos crecientes de inestabilidad del sistema nervioso central culminando en gran mal en forma convulsviva (tres enfermos) o llegando a los linderos de franca psicosis, tres enfermos). Las pruebas psicológicas del grupo “normal” (o sea los que no mostraron signos evidentes psiquiátricos), no mostraron alteraciones significativas en la conducta y en la actitud en el curso del tratamiento. Los reiterados EEG fueron normales salvo en un caso a pesar de la aparición de ataques en tres. Algunas de las dificultades que se encuentran para determinar el papel de la cicloserina como causantes de estos cambios se describen y se presentan casos típicos así como los respectivos niveles sanguíneos de la cicloserina.

Parece que en cualquier intento en el futuro para determinar la toxicidad de la cicloserina será esencial obtener un grupo de casos tan cerca de lo normal como sea posible y mientras tanto, el tratamiento con Cicloserina en las personas con trastornos psiquiátricos debe emprenderse con considerable precaución.

RESUMEN

Sur 30 malades traités par la cyclosérine, la moitié montrèrent quelque manifestation d’altérations psychiques ou neurologiques plus ou moins importantes. Chez six d’entre eux, apparurent des troubles sévères manifestés soit par des signes grandissant d’instabilité du système nerveux central, pouvant aller jusqu’à la crise épileptique (trois malades) ou par des psychoses ébauchées ou caractérisées (trois malades).

Les résultats des tests psychologiques pratiqués sur le groupe de malades normaux (c’est-à-dire ceux ne montrant pas de symptômes psychiatriques évidents) ne montrèrent pas d’altérations significatives de l’humeur ou de
l'attitude pendant la durée du traitement. Des électroencéphalogrammes répétés furent normaux, sauf dans un seul cas, malgré l'apparition des attaques chez trois malades. Les auteurs décrivent quelques-unes des difficultés auxquelles on se heurte pour pouvoir affirmer l'action de la cycloserine à l'origine de ces troubles, et en présentant des exemples typiques, avec des éléments fournis par l'étude du taux sanguin de cycloserine. Dans tout essai ultérieur pour évaluer la toxicité de la cycloserine, il semble essentiel de ne traiter autant que possible que les gens normaux. Durant cette période d'observation, le traitement par la cycloserine des personnes relevant de la psychiatrie devrait n'être entrepris qu'avec une prudence extrême.

ZUSAMMENFASSUNG

Von 30 unter Zykloserin gesetzten Patienten zeigte die Hälfte irgend welche Form psychischer oder neurologischer Veränderung von wechselnder Schwere. 6 zeigten schwere Funktionsstörung, entweder zum Ausdruck kommend in zunehmenden Anzeichen einer zentral-nervösen Labilität, die sich steigerte bis zu epileptischen Zuckungen, (3 Pat), oder zu ganz leichten oder auch völligen Psychosen (3 Pat.). Ergebnisse psychologischer Teste aus der "normalen" Gruppe, (d.h. jener, die keine zutage liegenden psychischen Symptome aufwiesen), ergab keine bedeutenden Veränderungen der Gemütslage und Geisteshaltung während des Behandlungsverlaufes. Wiederholte EEG's waren normal, von einem Fall abgesehen, trotz des Vorkommens von Anfällen bei 3. Es werden einige der Schwierigkeiten beschrieben, die eine Rolle spielen bei der Bedeutung des Zykloserins für das Zustandekommen dieser Veränderungen, und es werden typische Fälle vorgestellt, zusammen mit Zahlenwerten hinsichtlich der Zykloserin-Blutspiegelwerte. Für alle zukünftigen Versuche der Bestimmung der Toxizität des Zykloserins dürfte es wesentlich sein, eine möglichst grosse normale Fallzahl zu erreichen, und während solcher Versuche sollte die Zykloserin-behandlung von psychisch gestörten Personen nur unter besonderer Vorsicht erfolgen.

REFERENCES