

Fossil Basidiomycetes

R. L. Dennis writes [*Science* **163**, 671 (1969)], "The presence of clamp connections and saprophytism are thought to be features of advanced Basidiomycetes," and cites G. W. Martin [*Mycologia* **37**, 527 (1945)] as authority. On the contrary, Martin writes (p. 532), "The Tremellales [mostly saprobic, and with clamp connections in many species], more than either the Uredinales [parasites, without clamp connections] or Ustilaginales (parasites, rarely with clamp connections) retains the largest number of primitive characters." The whole argument and conclusions of the author cited are opposed to the statement for which, in an otherwise excellent paper, they are cited as support.

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Intramuscular Chlorpromazine and Creatine Kinase: Acute Psychoses or Local Muscle Trauma?

Meltzer (1) found an increase of serum creatine phosphokinase (CPK) and aldolase activities in acutely psychotic patients. He suggested that disruption of the functional integrity of the central nervous system produced mental symptoms and the endogenous process or agent which causes the in-

creased activity. He stated that neither physical exertion nor the administration of phenothiazines was related to the increased enzyme activity.

We assayed serums from 58 patients (successive admissions) for creatine kinase activity (2) (normal values, 12 to 58 I.U./liter). Five of the 25 acutely psychotic patients had CPK levels higher than 60 I.U./liter; three of the five had received intramuscular chlorpromazine within 72 hours before the assay. Of the 33 who were not acutely psychotic, two had CPK levels higher than 60 I.U./liter, although neither had received the drug intramuscularly. Of the 51 patients with CPK levels below 60, only one had received the drug in the preceding 72 hours. None of the patients had received intramuscular injections of any other drugs.

These observations suggested that intramuscular injection of chlorpromazine might cause the elevated CPK activity in serum. We, therefore, did the following study. Six rabbits received the drug intramuscularly, three received physiologic saline intramuscularly, and three received an intramuscular injection of the vehicle of a commercial chlorpromazine preparation. All CPK activity was shown to be of the muscle type by gel electrophoresis (3).

After the injection was given, the mean CPK activity of the group injected with chlorpromazine was significantly greater than the means for the other groups and the means of all groups before injection (Table 1). There were no significant differences between the means of all groups before injection, or between the means of the saline group before and after injection. The increase in CPK activity after injection was attributed to the intramuscular effect of chlorpromazine because there was no significant difference between the means of the saline and vehicle groups after injection ($P > .15$) even though there was a small but significant increase in the mean of the vehicle group after injection. The mean CPK activity of the chlorpromazine group returned to normal (84 ± 13) in 6 days, and this group was again given chlorpromazine (0.5 ml intramuscularly). The mean activity obtained as soon as 18 hours later (967 ± 163) was again greater ($P > .001$) than the activity before injection.

This increase in CPK activity after injection of chlorpromazine is therefore due principally to the drug. Pa-

tients have been reported to have elevated serum CPK concentrations after exercise (4) and after needling for electromyography (5). Chlorpromazine causes local irritation (6), and injection of irritating drugs can elevate serum CPK (7). Bengzon *et al.* found that elevated CPK concentrations in acutely psychotic patients returned to normal when the patients were started on phenothiazine therapy (8). Although their findings seem contradictory with ours, they did not state in their paper that any of their patients had received phenothiazine intramuscularly. Another recent report (9) states that alcoholics treated for acute withdrawal had elevated CPK, but whether intramuscular injections were given to these patients is not mentioned. Since intramuscular phenothiazines may cause high serum CPK concentrations in some patients, this source of enhanced serum enzyme activity needs further evaluation before interpretations of elevations in serum enzyme activities in patients can be made.

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Warnock and Ellman imply that the increase in creatine phosphokinase (CPK) and aldolase activity in acutely psychotic patients (1, 2) could be due to intramuscular injection of phenothiazines rather than its being a curious and significant manifestation of the acute psychotic process in some psychotic patients of all diagnostic types.

I too have noted that some patients

Table 1. Elevation of the serum CPK activity in rabbits (New Zealand strain, males, 2 to 3 kg) injected with chlorpromazine. Creatine phosphokinase activity (2) is expressed in international units (I.U.) per liter. The CPK activity before injection was determined on each of the 3 days immediately before treatment, and CPK activity after injection was obtained 18 hours after treatment. All injections were given intramuscularly. One group received 0.5 ml of a commercial preparation of chlorpromazine hydrochloride (Thorazine, 25 mg/ml); another received 0.5 ml of sodium chloride (U.S.P., 9 mg/ml); and a third received 0.5 ml of the aqueous vehicle which is used for the intramuscular injection of chlorpromazine (ascorbic acid, 2 mg/ml; sodium bisulfite, 1 mg/ml; sodium sulfite, 1 mg/ml; sodium chloride, 1 mg/ml; benzyl alcohol, 2 percent); Cpz, chlorpromazine.

Treatment	Rabbits (No.)	CPK activity before injection	(Mean $\pm$ S.D.) after injection
Cpz	6	88 $\pm$ 29	1092 $\pm$ 260*
Saline	3	95 $\pm$ 48	77 $\pm$ 35
Vehicle	3	118 $\pm$ 58	408 $\pm$ 280†

* Significantly higher than the mean before injection ($P < .001$; two-tailed *t*-test). † Significantly greater than the mean before injection ($P < .01$; two-tailed *t*-test).

have increased activity of CPK after receiving intramuscular injection of Thorazine but that other patients do not. For example, a girl with acute schizophrenia, who had not had any intramuscular injections, showed increased activity of CPK at admission which declined to normal limits 6 days later. She was then given 50 mg of Thorazine intramuscularly 2 weeks after admission. On the morning before the injection, CPK activity was 25 I.U./liter; 4 hours after the injection it was 22 I.U./liter, and 16 hours later, 22 I.U./liter (3). This same patient was given three subsequent intramuscular injections of Thorazine, 25 mg each, which also produced no change in serum CPK activity. I have specifically noted this lack of effect in seven other patients. Intramuscular injections of other materials only occasionally produce any change in serum CPK activity, and this is usually about 50 to 100 I.U./liter.

However, I have also observed considerably increased CPK activity following intramuscular injections in some individuals. An acutely psychotic 23-year-old female had normal CPK activity for 2 weeks, but on the 2 days following an intramuscular injection of Thorazine (25 mg) CPK activity was 242 I.U./liter and 134 I.U./liter. An acutely schizophrenic male who had had no injections or medication of any kind to the best of my knowledge had CPK activity of 375 and 495 I.U./liter on the first 2 days of hospitalization. In the evening of the second day, he was given Thorazine (50 mg) intramuscularly, and on the third morning of hospitalization, CPK activity rose to 1200 I.U./liter. While this was temporally contingent upon the injection, it should be pointed out that before the injection he was becoming much more disturbed and his CPK activity was rising.

None of the acutely psychotic patients reported by us had received any intramuscular injections before the taking of the blood sample with peak CPK activity; one patient subsequently received Thorazine intramuscularly (1). In our current studies, 24 of 37 acutely psychotic patients and none of 94 nonpsychotic severely disturbed psychiatric patients had increased activity of CPK (4). These patients were from a larger group of patients admitted to the Illinois State Psychiatric Institute and Billings Hospital of the University of Chicago and represent those in whom the possibility of any

intramuscular injections could be excluded. Thus, one can find increased activity of CPK in acutely psychotic patients who have never received intramuscular medications; but where an intramuscular medication has been given, an increase in CPK activity may be due to the injection itself. Approximately 20 percent of patients who receive intramuscular injections of Thorazine subsequently develop CPK activity. Oral phenothiazines are not associated with any increase or decrease in the activity of CPK in acutely psychotic patients.

It may be possible to distinguish between the two causes of increased activity of CPK under consideration. I have noted that the increases in CPK activity in humans due to intramuscular Thorazine tend to last 2 to 4 days, whereas the increases which occur presumably as part of the acute psychotic process tend to last 10 to 14 days; in one case increased activity persisted 51 days. We have found no increases in serum aspartate aminotransferase (glutamic oxalacetic transaminase) and serum lactate dehydrogenase activity associated with the increased CPK activity after intramuscular injection of Thorazine which is the same as in the acute psychoses (1). In any event, investigators of the serum enzyme changes in acute psychoses should obtain serum samples before giving intramuscular injections.

The small proportion of acutely psychotic patients in which Warnock and Ellman found increased CPK activity, 5 of 25, of which three may have been due to intramuscular injections, is significantly lower than that I have found in three studies: 14 of 16 in a study at the National Institutes of Health (1), 24 of 39 in a *blind* study at the Massachusetts Mental Health Center (5), and 24 of 37 in Chicago (4). It is also less than that reported by Schiavone and Kaldor and by Bengzon (2). There are at least four possible factors to consider for this difference: (i) the patients reported by Warnock and Ellman were mainly chronically psychotic patients experiencing an acute exacerbation of their illness, not the acute-type patient I have described; (ii) there had been a long delay between the onset of the acute psychosis and the time the blood samples were obtained; (iii) not all unequivocally acutely psychotic patients (unpublished data) from whom blood samples are taken within a few days of the onset of their psychosis and studied longitudinally thereafter will have mar-

kedly increased CPK activity; this may signify that there are two classes of acute psychotics with regard to the property of an increase in serum CPK activity accompanying the psychotic episode; the distribution of these groups may be uneven in studies with few subjects as it appears to have been in the NIH study (biased toward CPK releasers) and perhaps in the group of patients reported by Warnock and Ellman (biased toward CPK nonreleasers); (iv) the possibility that the increased CPK activity is an artifact bearing no relation to the psychotic process and caused by some other confounding influence not yet discovered and not present in Warnock's and Ellman's patients.

With regard to the rabbit studies reported by Warnock and Ellman, the dose of Thorazine given—4.2 to 6.2 mg/kg—is five to ten times the usual human intramuscular dose; and the volume injected (0.5 ml) into a small rabbit muscle is probably 15 to 30 times as large as a 1- to 2-ml injection into a human muscle. I have given rats chlorpromazine in saline as well as Thorazine in intramuscular doses from 0.5 to 10 mg/kg, in a volume of 0.05 ml, and killed them from 4 to 16 hours later; I found slight change in serum CPK activity. Part of the discrepancy may be due to species variation and part to significant variation in the local trauma from the injection. The release of CPK from rat muscle does not appear to be a pharmacologic property of chlorpromazine, for I have observed no increase in CPK activity in rats given chlorpromazine intraperitoneally or from rat muscle incubated with chlorpromazine in vitro.

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3. CPK was determined by the same method I used in my previous publications, which was also used by D. G. Warnock and G. L. Ellman [*Science*, this issue]. The upper limit of normal that I currently accept is 80 I.U./liter for admission samples and 50 I.U./liter for samples from inpatients.
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