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Correspondence

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CREATINE PHOSPHOKINASE AND PSYCHIATRIC ILLNESS

DEAR SIRS,

The recent report by Cunningham *et al.* in your January issue (124, 87–91) implies that finding increased serum creatine phosphokinase (CPK) activity in only 9 of 296 psychiatric patients (3 per cent) without 'accepted' possible causes of increased serum CPK activity is a refutation of the claims of myself and colleagues in seven publications of six different patient groups, which have been supported by ten other published investigations (see Meltzer, 1974; Foster and Kupfer, 1973), that serum CPK activity is elevated in most acutely psychotic patients who have been studied in the earliest days of their psychoses.

There are many possible reasons for the findings of Cunningham and his co-workers. Firstly, the claims I and other investigators have made of increased serum CPK activity in psychiatric patients have been almost exclusively confined to patients with *psychotic* symptoms. The Cunningham study does not separate patients into psychotic and non-psychotic groups. Conceivably, the percentage of acutely psychotic patients with increased serum CPK activity could have been as high in the Cunningham study as previously reported in other studies.

Secondly, my previous studies have emphasized the need to study acutely psychotic patients with very recent onset of psychotic symptoms—preferably no more than one week, and to study them repeatedly throughout their stay in hospital, since about as many patients first have increased CPK activity during periods of further decompensation in the hospital as have increased CPK activity at admission. We have also found that intensity of psychotic symptoms is highly correlated with increased serum CPK activity. No data are presented by Cunningham *et al.* to the time of onset of the illness of those patie who were psychotic; the severity of symptoms is n ommented on; and only one serum CPK sample, obtained at admission, was studied. All three factors could greatly contribute to the small percent- : of patients with elevated serum CPK activity.

Thirdly, Cunningham and his co-workers consider that in none of the patients with CPK increases who had had intramuscular injections could the CPK increases be associated with psychosis *per se*. We have shown that 8 of 14 (57 per cent) patients given a 50 mg. intramuscular (i.m.) injection of Thorazine[R] did not have increased serum CPK activity at any time during the next five days (reviewed in Meltzer, 1974). The decision to reject all patients who had *any* injection within one week of admission as possibly having an increase due to psychosis *per se*, while justifiable in some respects, is designed to produce the maximum number of false negatives. Since the patients most likely to receive i.m. injections in a psychiatric hospital are usually the severely disturbed acutely psychotic patients who are most likely to have increased serum CPK activity, it is necessary to make a special effort to reduce the use of the i.m. route of medication in a study of serum CPK activity so as to avoid elimination of a majority of the most relevant subjects from the study. The absence of such an effort by Cunningham *et al.* undoubtedly reduced the percentage of patients with increased serum CPK activity not due to 'accepted' causes.

Fourthly, Cunningham *et al.* relied on their clinical laboratory for CPK determinations. This laboratory utilizes one normal range of serum CPK activity for all humans (25–145 mU/ml.). It has been established beyond any doubt in numerous publications that serum CPK levels vary by sex, females generally having serum CPK activity 40–60 per cent lower than males. The upper limit of normal for females, using the method employed by Cunningham *et al.*, has been estimated at 97 mU/ml. (Miyada, Nakamura, Boyko, 1972). Thus the female patients in this study were not tested against the appropriate upper limit, and this could have led to many false negatives.

The final possibility to explain the small percentage of elevated serum CPK levels in this study is laboratory error. Clinical laboratories, after all, are far from ideal for research purposes. CPK determinations are open to many sources of error. It is extremely easy to inactivate CPK. Precautions must be taken to restore some of the lost activity due to oxidation of

sulfhydryl groups before determining the enzyme activity. Cunningham *et al.* say that the study was performed shortly after the Barnes Hospital laboratory began determining CPK activity. No data are presented about the accuracy and reliability of the laboratory's determination at that time. Farina, Litwinko and Bremner (1973) have called attention to inaccuracies of 30–70 per cent in CPK reference sera for the Auto-Analyser method employed by Cunningham *et al.* Such errors rarely occur in a research laboratory which is devoted to high accurate and reliable determinations of selected biological variables. There is no way of ascertaining whether major errors of this type occurred in the Cunningham study, but they certainly could have.

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DEAR SIR,

We do not claim that we have refuted Professor Meltzer's findings; rather that our study fails to confirm them. We began investigation with the hope that some small group of rigorously defined patients would show consistent elevations of CPK. That none did surprised us.

We agree with Professor Meltzer that one feature of our research design, namely failure to withhold intramuscular injections, rendered our study an inadequate test of his claim. However, the bulk of research on this subject—research which Professor Meltzer cites in support of his position—not only incorporates this same defect of design but is compounded by other deficiencies. For instance, the established relationship between alcohol and elevated CPK has been largely ignored in CPK investigations. Chronic heavy alcohol intake is very common among psychiatric in-patients, including those with an admitted diagnosis other than alcoholism.

Regarding the criticism that we do not provide the time of onset of illness, we would suggest that a glance at Table II indicates such information is available.

The problem of who is psychotic and who is not is perennial. Use of the term has been confusing for at least a half a century. Renard Hospital is an acute treatment centre in an urban setting. Approximately a quarter of our patients are admitted with hallucinations, delusions or what is sometimes described as 'loss of contact with reality'. We investigated these patients as well as others.

Professor Meltzer's hypothesis has not been refuted. But it has not been confirmed, and will not be until prospective studies are accomplished in which intramuscular injections are withheld, patients with other potential causes of elevated CPK are carefully removed from study, and rigorous criteria for establishing the diagnosis of 'acute psychosis', dating its onset and evaluating its intensity are developed.

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