cide in mice; determination of the LD_{50} value was hindered by very erratic response.

Matacil (*7*) (4-dimethylamino-3-tolyl methylcarbamate) produced symptoms different from those of other carbamates; eight of the ten mice fed 130 to 200 mg/kg became lethargic and stuporous and died 12 to 20 hours later; because of the prolonged symptoms and delayed death, the effectiveness of TEAC as an antidote could not be ascertained. The time at which the TEAC is administered as a treatment may be critical (*8*).

Mice fed a lethal dose of the noncarbamate Parathion (*9*) (*O,O*-diethyl-*O*-*p*-nitrophenyl phosphorothioate) died in convulsions in 10 to 15 minutes, with or without TEAC injected as an antidote. After treatment with a lethal dose (50 mg/kg) of the noncarbamate nicotine, mice injected with TEAC at 20 mg/kg did not show the typical nicotine syndrome of convulsions, curare-like paralysis, and death within 10 minutes.

Tetraethylammonium chloride appeared to be a safer and more effective antidote than atropine sulfate for some insecticide intoxication; TEAC blocks transmission at autonomic ganglia, and the effects are mutually antagonistic to adrenergic and cholinergic substances (*10*); it shows promise as an antidote because of its therapeutic effect and because its side effects were less than those of atropine sulfate at the concentrations tested.

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Creatine Kinase and Aldolase in Serum: Abnormality Common to Acute Psychoses

Abstract. *Activity of creatine kinase and aldolase in serum increased in 14 of 16 patients with recent onset of a psychotic reaction, and in five of six patients treated with psychotomimetic drugs. There was either no increase of these enzymes or a slight increase in severely agitated (or depressed) nonpsychotic hospitalized patients and chronic psychotic patients. The increase of the enzymes preceded the onset of the acute psychotic symptoms in at least three cases, was highest during the first 2 weeks of a psychotic episode, and sometimes recurred throughout the illness, particularly at times of stress. The creatine kinase in the serum is primarily of the muscle type.*

Incidental to a study of creatine kinase (CPK) (E.C. 2.7.3.2) in the serum in neurologic disorders, Schiavone and Kaldor found that the activity of the enzyme in the serum of nine of 24 schizophrenic patients had increased (*1*). In investigating changes in the serum during treatment with psychotropic drugs, Bengzon *et al.* found that in 30 of 60 acutely psychotic patients the activity of CPK and aldolase (E.C. 4.1.2.7) was increased before treatment. After the patients were treated with phenothiazines, the activity returned to normal within 1 week in females and within 4 weeks in males (*2*). I now report on the incidence of increased activity of these enzymes in the serum of schizophrenic and other psychiatric patients, and the results of a study on the sources of the increase.

This study was made on 16 acutely psychotic patients, 14 chronically psychotic patients, and 11 patients who were not psychotic by clinical evaluation or psychological testing but who required psychiatric hospitalization because of severe agitation, anxiety, or depression. The clinical status of the patients and other clinical data apart from biochemical data were ascertained (*3*). The CPK and aldolase were determined spectrophotometrically by a series of coupled enzyme reactions resulting in the reduction of nicotinamide nucleotides (*4*). In our laboratory, normal amounts of CPK in serum are 10 to 50 I.U./liter for men and 10 to 40 I.U./liter for women, whereas those of aldolase are 200 to 400 μmole ml^{-1} hr^{-1}.

In nine of 11 acute schizophrenic patients, a significant increase in activity of CPK and aldolase in serum was found at some phase of their clinical course (Table 1) (*5*). Four patients suffering from the other acute psychoses, including three manic-depressive patients in the manic phase and one patient with acute psychotic depression, also exhibited greatly increased activity of these enzymes. Furthermore, one patient with periodic catatonia had abnormally high activity of these enzymes during the first week of a catatonic episode, whereas previously it was normal (*6*).

Six of the 16 acutely psychotic patients were quite disturbed at the time of admission, and their serum had increased enzyme activity which returned gradually to normal, usually within 10 days or less. One patient, though admitted to the hospital in a distinctly psychotic state 3 days after the abrupt onset of his symptoms, had normal activity of CPK and aldolase at that time, but it increased dramatically 3 days later as his clinical condition temporarily worsened. Seven of the patients were first studied in a relatively quiescent phase of their illness, and their serums initially had normal enzyme activity. These patients had a recurrence or exacerbation of an acute psychotic state, at which time both enzymes increased sharply. With three of these patients, blood samples taken prior to the first clinical evidence of recurrent decompensation established that the enzyme increase preceded the first clinical detection of the psychotic state by 8 days in one case and by 4 days and 2 days in the others. In one of these patients, the enzyme increase began at the time of the first home visit in 2 months, and in the second patient it began when he was given community privileges and urged to find employment. In general, the increase in activity of CPK and aldolase in the serum was greatest before or at the outset of one of these recurrent episodes and gradually returned to normal or near normal in 2 to 5 weeks. No differences were noted between enzyme activity in males and females. However, transient increase in this activity recurred in some patients throughout their hospitalization, even though they were no longer considered to be psychotic. This was particularly true of the period before discharge when the patients were experiencing the stress of making major readjustments to their life situations. One of the patients with normal enzyme activity throughout a lengthy and stormy

Table 1. Maximum increases of activity of CPK and aldolase in the serum of acute psychotic patients.

CPK (I.U./liter)	Aldolase (μmole ml^{-1} hr^{-1})
Paranoid schizophrenia	
900	875
824	850
24	249
950	2250
Undifferentiated schizophrenia	
900	729
241	519
200	809
24	256
Catatonic schizophrenia	
900	790
Schizo-affective schizophrenia	
260	750
600	898
Manic-depressive	
284	584
510	700
600	750
Psychotic depression	
350	1100
Periodic catatonia	
140	958

hospitalization was of the process type of schizophrenia; the other was transferred to the National Institute of Health 1 month after the onset of his psychosis and appeared to be recovered at the time of admission.

The 14 chronically psychotic patients and the 11 nonpsychotic anxious or depressed patients had normal activity of CPK and aldolase in serum throughout hospitalization, except for three chronic psychotic patients and two neurotic patients who had slight, transient increases of one or both enzymes (Tables 2 and 3).

A study of the effects of psychotomimetic drugs on CPK and aldolase in man is being conducted on a blind basis with the cooperation of Drs. W. Pahnke and A. Kurland of Spring Grove State Hospital, Towson, Maryland, who are using psychotomimetic drugs to treat alcoholic patients. Four of the first five patients and one normal volunteer, from whom blood samples were taken 24 hours after treatment with 450 μg of LSD (lysergic acid diethylamide) or 30 mg of dipropyl tryptamine, had an increased activity of CPK or aldolase. For example, the aldolase in the serum of one patient increased from 240 μmole ml^{-1} hr^{-1} prior to treatment to 780 μmole ml^{-1} hr^{-1} 24 hours after receiving 450 μg of LSD; it was normal when measured again 4 days later. Interpretation of these findings is difficult because chronic alcoholic patients may be particularly prone to release CPK under any kind of stress (*7*).

To understand why CPK and aldolase are increased in the acute psychoses and probably the drug-induced "model" psychoses as well, it is most important to determine from which tissue the enzymes in the serum come. Creatine kinase occurs almost exclusively in muscle and brain as distinct isoenzymes (proteins with the same enzymatic specificity which can be resolved into different molecular forms by physicochemical methods) (*8*). Using the procedure of Richtereich as modified for CPK isoenzymes by Dubo *et al.* (*9*), I found the CPK in the serums of acutely psychotic patients to be largely of the muscle type. Because small amounts of this type of CPK may be present in tissues other than muscle, this does not definitely establish muscle as the tissue source of the enzyme although muscle remains the most likely possibility.

A number of factors that could account for the apparent increase of CPK and aldolase activity in serum have been considered. No enzymatic activity was noted after the serums were heated to 65°C or after the substrate was omitted from the reaction mixture. Prolonged dialysis of serums with high and low activity from schizophrenic patients at 4°C had no effect, an indication that no small molecules were influencing the activity of these enzymes. The administration of phenothiazines could not be correlated with the increases in enzyme activity. There was no evidence for any of the other disorders with which increased CPK and aldolase activity have been associated (*10*). There was no systematic relation between catabolism, as evidenced by weight loss, and increased activity of CPK and aldolase; this is of interest because of the suggestion of Berlet *et al.* that the breakdown of muscle in schizophrenia serves to exacerbate the psychotic process initiated by some other mechanism (*11*).

Physical exertion, sometimes very minimal exertion, produces increased CPK and aldolase, particularly in people not athletically trained (*12*). Six of the acute patients, including one who was catatonic and another immobilized by severe depression, were physically quiet during the periods of increased enzyme activity. The four psychotic patients who were most hyperactive during my study did not show greater or more prolonged increases of CPK and aldolase than the rest of the group did. Glutamic oxoaloacetic transaminase (E.C. 2.6.1.1) and lactate dehydrogenase (E.C. 1.1.27) which are also increased after exercise were not increased throughout hospitalization, except in one patient with definite muscle trauma (*13*).

Table 2. Maximum increases of serum CPK and aldolase in chronic psychotic patients.

CPK (I.U./liter)	Aldolase (μmole ml^{-1} hr^{-1})
Undifferentiated schizophrenia	
17	217
23	137
26	302
22	256
97	374
10	193
25	207
19	146
91	269
19	261
Psychotic depression	
66	447
17	261
19	254
15	241

Our data suggest that stress is linked to the increased activity of these enzymes in serum in the acutely psychotic patients. The slight, transient increases in a few of the nonpsychotic and chronically psychotic patients may not be related to the increases in the acute patients, because a number of people in the general population have increased enzyme activity (*14*). It has been reported that the administration of ACTH (amount unspecified) has no effect on CPK and aldolase in the serum of man but increases aldolase activity in rabbit plasma (*15*). Corticotrophin gel (40 units) was administered subcutaneously to two patients. There was a slight increase of CPK and aldolase at 8 hours in one patient, but no changes were noted in the other, a formerly psychotically depressed patient who had much increased activity of CPK and aldolase when admitted to the hospital.

Table 3. Maximum increases of activity of CPK and aldolase in the serum of nonpsychotic psychiatric patients.

CPK (I.U./liter)	Aldolase (μmole ml^{-1} hr^{-1})
Anxiety reaction	
15	328
33	244
Cyclothymic personality	
24	300
Borderline state	
20	338
11	263
Agitated depression	
26	270
19	229
15	217
Retarded depression	
66	226
96	294
Situational turmoil	
18	232

The significance of the increased activity of CPK and aldolase in the serum of acutely psychotic patients regardless of diagnosis, as well as in patients receiving psychotomimetic drugs, remains to be determined. It probably represents increased permeability of the cell membrane of some tissue to these enzymes, but it could also be due to decreased clearance of these enzymes from serum (*16*). It is difficult to conceive of any direct relevance of these changes to the psychotic process without an implication of a change in brain function. There is a possibility that an increased cell permeability or decreased clearance from serum is the peripheral manifestation of a pathologic process occurring in the central nervous system, just as, in tetanus, tetanus toxin increases muscle cell permeability to CPK and aldolase and blocks specific inhibitory neurons (*17*). The finding that an increase in serum of muscle-type CPK occurs in the absence of gross muscle damage in a variety of disturbances of central nervous functioning, including some cases of brain trauma, brain tumor, meningitis, encephalitis, epilepsy, or cerebral vascular insufficiency (*1*, *9*, *10*, *18*), suggests that the acute psychotic syndromes could be much more closely related to organic brain disease than they were previously believed to be, and that some endogenous agent or process, activated or initiated by disruption of cerebral integrity, could affect the activity of CPK and aldolase in the serum. Investigation of the cause of increased enzyme permeability or decreased clearance of enzymes from serum in human tissues which may be available for direct study, or in animal models which could be developed, may permit some approach to central nervous system events which could occur in the acute psychotic state.

Our data, in agreement with clinical experience, suggest that in acute psychoses the attempt to meet a stressful life situation disrupts the functional integrity of the central nervous system and leads both to mental symptoms and the endogenous agent or process which produces the increased activity of CPK and aldolase. A common specific mechanism leading to the release of muscle enzymes in the acute psychoses, the drug-induced "model" psychoses, and perhaps in other altered states of consciousness, such as those subsequent to sensory deprivation and sleep deprivation, indicates a fundamental biological relation between these states which was previously suspected but not proved. The data indicate that determination of CPK and aldolase activity in the serum might be of value as a chemical test for acute psychosis as well as in the prediction of incipient decompensation in patients being studied over a period of time.

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Protein Synthesis in the Hippocampal Pyramidal Cells of Rats during a Behavioral Test

Abstract. *Protein synthesis was studied in the pyramidal nerve cells of the CA3 region in the hippocampus of rats during a behavioral test involving transfer of handedness. A new electrophoretic technique was used for separation of 10^{-7} to 10^{-9} gram of protein and radiometric determination of the various protein fractions. After interventricular administration of ^{3}H-leucine, protein synthesis of two fast-moving fractions was significantly higher bilaterally in the hippocampus of the trained rats. There was also a trend to lateralization of the highest protein synthesis to the learning side.*

The hippocampus modulates and integrates reticular patterns of activation and thalamic patterns of projection during learning. It seems to integrate patterns of ascending activation in subcortical regions with cortical activity. The emotional part involved in the establishment of new behavior seems to be functionally integrated by the hippocampo-limbic region. The stimulatory level is low in the hippocampus, and a burst of activity in it easily spreads to other parts of the limbic system and affects various emotional modalities, such as aggression and regulation of the hormonal outflow from the hypothalamus. Impulses from viscera and those sensed as pain seem to reach the hippocampus via caudal parts of the reticular formation. Bilateral destruction of the hippocampus in man results in severe memory defects, inability to learn, and dysfunction of the mechanisms for thought processes (*1*). Experiments with electrodes implanted in the hippocampus have shown definite changes in the electrical pattern during learning (*2–4*). It also seems that when some new element is introduced into a learning situation, the electrical response in the hippocampus is increased. As the new element becomes familiar, there occurs a decrease of response which is obvious in the hippocampus (*2*, *3*). Penfield (*5*) has concluded that in man the recording of current experience is impossible without the hippocampus. Flexner and collaborators (*6*) have correlated behavior in mice with protein synthesis which was inhibited to various degree by puromycin. Destruction of long-term memory was found when protein synthesis was inhibited by 80 percent in the hippocampus, the tem-