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General Articles

Muscle Abnormalities in Acute Psychoses

Herbert Y. Meltzer, MD, and Ronald Moline, MD, Chicago

SERUM creatine phosphokinase (CPK) and aldolase activities are increased in many acutely psychotic patients of a variety of diagnostic types.[1-3] CPK exists in three molecular forms (isoenzymes). Type I is found almost exclusively in the brain, type II in cardiac muscle, and type III in skeletal and cardiac muscle.[4] Much smaller amounts are present in many tissues.[5] Only the type III isoenzyme of CPK was found in the sera of psychotic patients.[1,2] A number of possible causes of an increased activity in serum of type III CPK have been evaluated: orally or intramuscularly administered psychotropic medications[2,6]; physical activity[2,7]; severe emotional distress not part of a psychotic process[2]; weight loss[2,8]; hypersecretion of steroids[2] or epinephrine[8]; and muscle tension.[7] These have been considered to be not responsible for the increased serum enzyme activity in most acutely psychotic patients. Increased activity of serum CPK was also reported in approximately 25% of the first-degree relatives of acutely psychotic patients but the levels were modest and could have been related to physical activity.[2,9]

Since increased serum CPK activity is one of the most sensitive indices of primary muscle pathological abnormality[10] it seemed possible that an abnormality of muscle could be responsible for the increased serum CPK levels in acutely psychotic patients and their first-degree relatives. To evaluate this hypothesis, the serum CPK and aldolase activity of a group of acutely psychotic patients was determined longitudinally. The possibility of an abnormality of muscle in these patients in comparison to controls was evaluated in the following ways: the isoenzyme(s) of CPK in sera was determined; other serum enzymes which are or might be increased in muscle disease (and, as a check of specificity, in liver disease) were assayed in sera with increased activity of CPK; open muscle biopsies were performed and the excised muscle evaluated with histochemical and light and electron microscopic methods on a blind basis for morphologic evidence of myopathy; biochemical studies were performed on the muscle specimens; the amount of creatine and the creatine to creatinine ratio in 24-hour urine collections were determined; and the effects of a standardized exercise test on serum enzyme activity were ascertained. The rationale behind most of these approaches is immediately apparent. The urine determinations were performed because creatinuria and an increased creatine to creatinine ratio are frequent concomitants of muscle disease of a wide variety of types.[11] The activity of serum enzymes following a standardized exercise test was determined because this technique has been useful in demonstrating the minimal myopathy in the carriers of Duchenne dystrophy.[12]

The effects of the standardized exercise test on serum enzymes in acutely psychotic patients has been reported.[7] A preliminary report of abnormalities of muscle demonstrated with histochemical methods in some acutely psychotic patients has been published elsewhere.[13] In companion papers, additional evidence of myopathic changes in the muscle of acutely psychotic patients is presented and discussed.[14,15]

Here we wish to report the serum CPK and other enzyme activities of the biopsied patients, relatives, and psychiatric patient controls, some basic biochemical characteristics of the muscle of the psychiatric patients possibly relevant to increased levels of

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From the Department of Psychiatry, University of Chicago Pritzker School of Medicine (Dr. Meltzer), and the Illinois State Psychiatric Institute (Dr. Moline), Chicago.

Reprint requests to Department of Psychiatry, University of Chicago, 950 E 59th St, Chicago 60637 (Dr. Meltzer).

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CPK in serum, and the excretion of creatine and creatinine in the urine specimens of acutely psychotic patients. The significance of the accumulating evidence for muscle abnormalities in acutely psychotic patients and their relatives will be discussed.

Methods

Subjects.—Ninety-six psychiatric patients admitted to a research ward at the Illinois State Psychiatric Institute participated in some or all parts of this study. Clinical diagnosis was established by two psychiatrists and a psychologist without knowledge of serum enzyme activity or muscle biopsy. There were no signs, symptoms, or laboratory evidence of other diseases which might increase serum CPK or aldolase levels, eg, Duchenne dystrophy, hypothyroidism, myocardial infarction, or hepatitis.

Seventy-five parents, siblings and children of the acutely psychotic patients participated in various aspects of this study. None had overt psychiatric illnesses or previous histories of psychiatric hospitalization, except where noted.

Serum Enzyme Determinations.—Serum CPK activity was determined by the method of Rosalki,[16] using a commercially available enzyme kit on five samples per week for almost all hospitalized patients in this study. Enzyme activity is reported as international units (IU) per liter at 30 C. Commercially available sera of known enzymatic activity was used to standardize the assay. As an additional check on the presence of increased CPK activity, the sera with increased activity were sometimes assayed with the method of Kuby et al[17] which employs an entirely different principle from the Rosalki technique.

Aldolase activity was determined by the method of Bruns,[18] using a commerically available enzyme assay kit, on admission samples or some samples with increased CPK activity (pathologically abnormal sera) for nearly all patients in this study. Aldolase activity is reported as milliunits per milliliter at 25 C. Lactic dehydrogenase (LDH) was determined by the method of Wacker et al,[19] aspartate aminotransferase (GOT) by the method of Karman et al,[20] phosphohexose isomerase (PHI) by the method of Bogdansky,[21] glutamic dehydrogenase (GlDH) by the method of Schmidt,[22] malic dehydrogenase (MDH) by the method of Siegel and Bing,[23] isocitric dehydrogenase (ICDH) by the method of Wolfson and Williams-Ashman,[24] and α-hydroxybutyrate dehydrogenase (α-HBDH) by the method of Rosalki and Wilkinson.[25] The activity of these enzymes was determined in 15 to 50 pathologically abnormal sera from acutely psychotic patients. Normal limits for serum CPK activity were obtained from 150 healthy blood donors.[3] Normal limits for the activity of the other enzymes were obtained from published reports utilizing the same methods and corraborated by assaying sera of nonpsychotic psychiatric patients who were free of organic disease and not receiving any psychotropic medication.

Muscle Biopsies.—All patient subjects received chlorpromazine (Thorazine), meperidine, and promethazine (Phenergan) one-half hour before the biopsy, which was performed with the subjects under 2% lidocaine with epinephrine local anesthesia. Only the skin was infiltrated, never the muscle. No intramuscularly administered medication was ever given to the biopsied limb. Two pieces of muscle, each approximately 250 mg, were excised from each subject and frozen within one minute of excision in isopentane cooled in liquid nitrogen. The biopsies were kept at −10 C until the following studies were done (generally within 24 hours).

One piece of frozen muscle from each of 28 subjects was thawed, blotted, rapidly weighed, and thoroughly homogenized in a Potter-Eveljhem apparatus in 20 volumes of ice-cold sucrose (0.25M). Unbroken cells and debris were removed from the homogenate by centrifuging at 700 g for ten minutes at 5 C. The supernatant from this fraction (supernatant 1) was centrifuged at 10,000 g for 20 minutes. The pellet from the second centrifugation, which was a crude mitochondrial fraction, was suspended in ice-cold sucrose (0.25M). CPK activity and total protein content were determined in the two supernatants and the mitochondrial fraction. For determination of CPK activity, the various fractions were diluted with isotonic saline into a range where the change in optical density at 340 mμ in five minutes was linear.[16] Total protein was determined by the method of Lowry et al.[26] The isoenzymes of CPK were determined by agar gel electrophoresis.[27] Total glycogen in a separate piece of frozen muscle was determined by the method of Montgomery.[28]

Urine Studies.—From five to ten 24-hour urine collections were obtained from four male and nine female acutely psychotic patients with increased CPK activity. The collections were obtained at random times during the course of the illness, including some periods when serum CPK activity was increased. For comparison purposes, collections were obtained from six male and four female nonpsychotic patients.

The patients all received the regular hospital diet which contains approximately 115 gm of protein per day. Creatine was determined by the enzymatic method of Tanzer and Gilvarg[29] as modified by Marymont et al.[30] Creatinine was determined by the method of Van Pilsum.[31]

Results and Comment

Serum CPK Activity in Acutely Psychotic Patients.—Serum CPK activity as determined by the Rosalki method was significantly increased (> 80 IU/liter) in 44 of 64 acutely psychotic patients, including 36 of 50 acutely schizophrenic patients, 2 of 6 manic-depressive patients, 2 of 4 involutional psychotic patients, and 2 of 4 patients with paranoid psychosis (Table 1). The serum CPK activity as determined by the Kuby method was also abnormal in those sera where the CPK activity by the Rosalki method was greater than 100 IU/liter (data not presented). The increased CPK activity was present in the admission sample of 35 patients. The first increase occurred only after admission in nine other patients. This generally preceded (No. = 4) or coincided with (No. = 5) major exacerbation of the psychotic process.

Table 1.—*Peak Serum CPK Activity (IU/Liter) in Acutely Psychotic Patients*

	Males		Females		
Acute Schizophrenia					
1. 3,522	9. 496	17. 132	1. 860	10. 215	19. 78
2. 1,534	10. 463	18. 111	2. 625	11. 210	20. 76
3. 1,530	11. 243	19. 76	3. 492	12. 205	21. 68
4. 1,170	12. 230	20. 68	4. 463	13. 154	22. 54
5. 917	13. 230	21. 55	5. 392	14. 150	23. 45
6. 796	14. 212	22. 50	6. 365	15. 140	24. 39
7. 618	15. 195	23. 32	7. 280	16. 135	25. 30
8. 496	16. 188	24. 28	8. 270	17. 113	26. 14
			9. 241	18. 80	
Manic-Depressive Psychosis, Manic-Phase					
	Males		Females		
	1. 44		1. 850	4. 59	
			2. 347	5. 36	
			3. 75		
Involutional Depression					
	Males		Females		
	1. 860		1. 428		
			2. 32		
Paranoid Psychosis					
	Males		Females		
	1. 122		1. 210		
			2. 196		
			3. 48		
			4. 35		

* 80 IU/liter is the 95% upper limit of confidence in our laboratory.

Table 2.—*Acutely Schizophrenic Patients With Persistent Increase in Serum CPK Activity*

Patient	Sex	No. of Samples	Period of Study (mo)	Mean (IU/Liter)	Range (IU/Liter)
1	F	90	13	107 ± 60	37-365
2	M	54	4	112 ± 89	32-496
3	M	41	4	73 ± 39	14-188
4	M	56	9	149 ± 151	38-496
5	M	47	3	116 ± 133	28-618
6	M	46	3	177 ± 231	49-917
7	M	63	4	107 ± 49	43-230

The magnitude and duration of the increased CPK activity in this sample of acutely psychotic patients was in general accordance with previous reports of these aspects of serum enzyme activity.[1-3] Of interest is the fact that in seven acutely schizophrenic patients the serum CPK activity was continuously abnormal or borderline abnormal, except for a few days, from the onset of hospitalization through discharge and follow-up care, a period ranging from 98 to 380 days (Table 2). The activity of other serum enzymes has not been studied for such prolonged periods in these subjects. Heretofore, persistently increased serum CPK activity had been found in some relatives of acutely psychotic patients, but not in the patients themselves. The enzyme levels in these seven patients, as in other acutely psychotic patients, were not constant throughout the period of study, but peaked at the time of exacerbation of psychosis. In one other patient the increased enzyme activity lasted for 40 days and then returned to normal.

Three patients with schizophreniform symptomatology induced by street drugs believed to be lysergic acid diethylamide (LSD) and which cleared rapidly had no

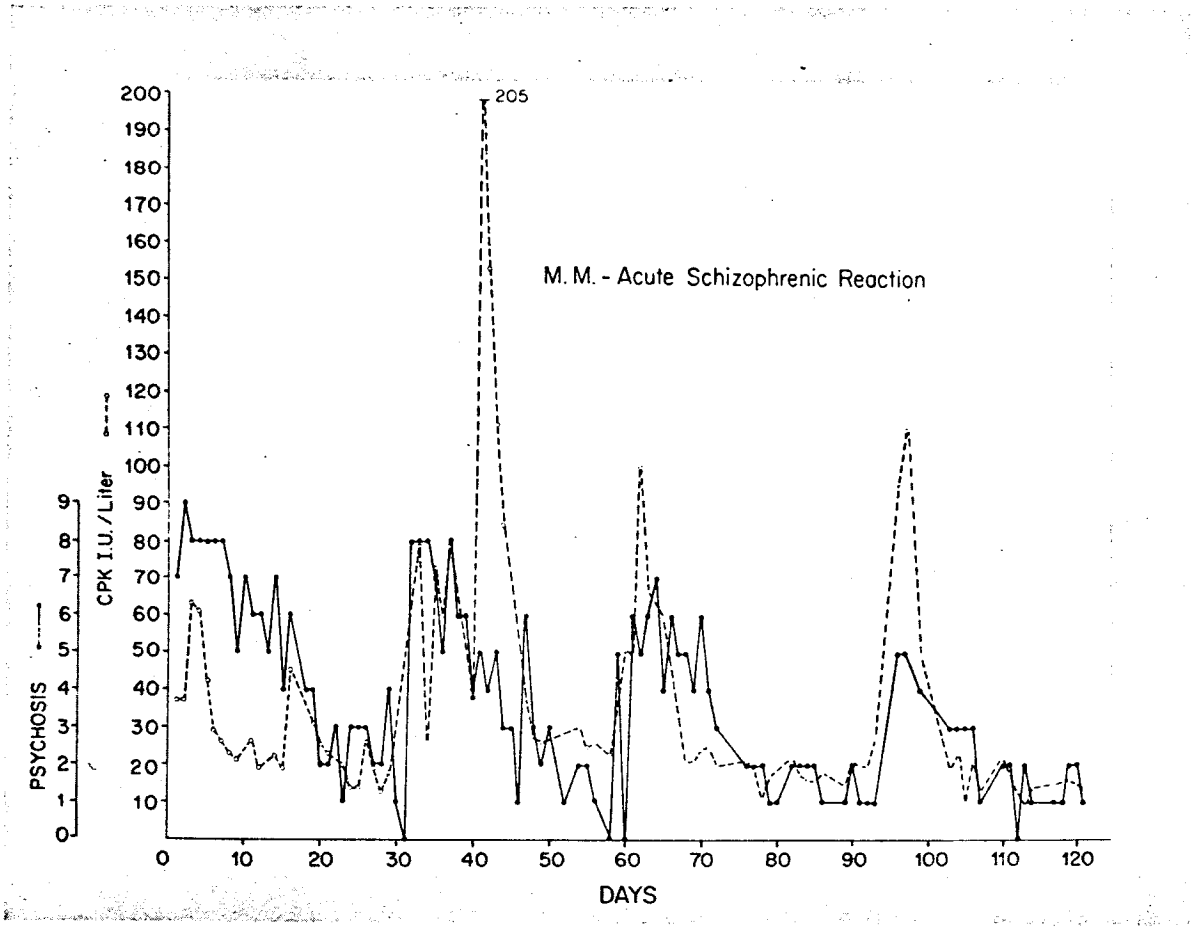

Fig 1.—Global rating of psychosis made by psychologist and nurse (on scale of 1 to 9) and serum CPK activity for an acutely schizophrenic patient.

increase in serum CPK or aldolase activity.[6] One patient, whose presumptive LSD experience was followed by four psychotic periods of a schizophrenic nature, separated by approximately four-week intervals, had increased CPK activity with each period of psychosis (Fig 1). Similar correlations between psychopathological disturbance and serum enzyme activity have been noted in many other acutely psychotic patients.[1-3] One patient with an acute psychosis secondary to amphetamine abuse had increased aldolase activity but normal CPK activity. This has been previously observed in some subjects receiving high doses of amphetamine (H. Meltzer et al, unpublished data) and in some sleep-deprived normal subjects.[32]

Acutely Psychotic Patients Without Increased CPK Activity.—The 20 acutely psychotic patients with no increase in serum CPK levels were not markedly different in clinical symptomatology from those with elevated enzyme levels. Their illnesses, in 17 of 20 instances, were of rapid onset, ie, within one to four weeks prior to admission. (In one previous report, the only first-break schizophrenic patient with normal serum CPK activity was a process-type schizophrenic).[2] The first serum CPK determination of 12 of these 17 patients was obtained within 72 hours of the apparent onset of grossly psychotic behavior and was determined five times per week thereafter. This should have been early enough and frequent enough to detect an abnormal increase of serum CPK activity had one been present. Two of these patients had a second acute psychotic period

in the hospital with no increase in serum enzyme activity. It appears, thus, that increased activity of CPK in serum is not an invariant concomitant of acute psychosis. A number of studies aimed at distinguishing the acutely ill patients with and without increased CPK activity are in progress. Preliminary studies using cognitive tests and a quantitative prognosis estimation have produced no significant differences (M. Loren and H. Meltzer, unpublished data). It should be pointed out that the normal levels of CPK activity in some acutely psychotic patients do not preclude increased release of CPK from muscle in some or all of these patients since a high rate of clearance of the enzyme from serum could neutralize the effect of the increased release on the overall level of enzymatic activity.

Table 3.—*Distribution of Serum CPK Activity in Relatives of Acutely Psychotic Patients*

	No. of Relatives With CPK Activity		
Relative	0-49*	50-80*	>80*
Fathers	8	6	0
Mothers	16	6	3
Brothers	4	4	5
Sisters	14	2	4
Sons	0	1	0
Daughters	2	0	0

* IU/liter.

Isoenzymes of CPK in Sera.—Only the type III (skeletal muscle) isoenzyme of CPK was detected in the sera of acutely psychotic patients. This suggests, but does not absolutely prove, that skeletal muscle is the source of the CPK in the sera of acutely psychotic patients. (The CPK isoenzyme in the brain of a deceased acutely schizophrenic patient was the brain type exclusively in all regions sampled. This would, if confirmed in other patients, definitely rule out the brain as the source of the CPK in the sera.)

Serum CPK Activity of Relatives of Acutely Psychotic Patients.—Serum CPK activity of 31 of 75 relatives of acutely psychotic patients was in the region of borderline increased enzyme activity (50 to 80 IU/liter) or beyond the 95% upper confidence limit for ambulatory people (80 IU/liter) (Table 3). The increases are present in parents and siblings of both sexes, as well as in the 14-year-old son of a manic-depressive patient. Some relatives of all types of acutely psychotic patients were found to have increased activity of CPK. The incidence of increased CPK activity in both male and female relatives is significantly different from that of previously reported groups of healthy, fully active, men and women at greater than the 0.001 level of confidence using a 1×3 χ^2 test (Table 4). As in previous groups of such relatives, the increased activity of CPK was present in all samples obtained from

Table 4.—*Distribution of Serum CPK Activity in Relatives of Acutely Psychotic Patients vs Normal Subjects*

	No. of Subjects With CPK Activity				
Subjects	0-49*	50-79*	>80*	χ^2	*P*
Normal males	60	16	2		—
Male relatives	12	11	5	35.74†	<0.001
Normal females	59	7	1		—
Female relatives	32	8	7	60.80†	<0.001

* IU/liter.
† χ^2 was determined by a 1×3 contingency analysis using the expected frequencies from the normal subjects.

Table 5.—*CPK Activity in Muscle Biopsies of Psychiatric Patients**

Subjects	IU/mg Protein†	IU/gm Tissue	% Total Activity
	Supernatant[1]		
Acute Psychotics (n=20)	10.7 (5.0)‡	1,620 (381)‡	—
Non-Psychotics (n=9)	11.9 (6.0)	1,580 (523)	—
	Supernatant[2]		
Acute Psychotics (n=20)	22.1 (12.0)	1,570 (591)	86.5 (21.3)
Non-Psychotics (n=9)	28.8 (6.5)	1,800 (1,114)	89.0 (19.0)
	Mitochondria		
Acute Psychotics (n=20)	6.1 (5.1)	53.2 (42.4)	3.1 (2.2)
Non-Psychotics (n=9)	6.9 (32.0)	61.8 (68.5)	3.8 (3.4)

* The means of each parameter for the acutely psychotic patients and nonpsychotic patients were compared with the Student's *t*-test with a correction for unequal variances where appropriate. There were no significant differences at at least the 0.05 level of confidence.
† See text for methods. Results are expressed in μmols of substrate transformed per milligram of extracted protein or per gram wet weight per minute.
‡ Numbers in parentheses are standard deviations.

a given individual over a three-month to one-year period. A depressed, nonpsychotic 19-year-old girl, hospitalized after her second suicide attempt, had numerous family members, including her mother, who were manic-depressive. She herself had serum CPK activity between 40 and 68 IU/liter in 44 samples obtained over a three-month period (mean, 52.4 IU/liter ± SD 8.4 IU/liter). The mean serum CPK activity in nonpsychotic women without family histories of psychosis is generally 15 to 30 IU/liter (H. Meltzer, unpublished data).

In three families, numerous family members had increased serum CPK activity. The serum CPK activity of two brothers of an acutely schizophrenic girl, who herself had a persistent increase in CPK activity, was usually greater than 350 IU/liter, which is higher than the peak CPK activity of approximately 50% of the acutely psychotic patients. The mother of this patient had a serum CPK activity greater than 150 IU/liter. Normal physical activity would not usually account for these findings in the family of this patient. Standardized exercise tests performed by eight of the relatives in this study indicated, however, that four of them had abnormally large increases in serum CPK activity following the exercise.[7] These findings could be an indication of a genetic factor in the increased serum enzyme activity of these acutely psychotic patients.[1,2]

Serum CPK Activity in Other Psychiatric Patients.—One of the eight chronically schizophrenic patients in this study had increased serum CPK levels. Serum CPK activity in this patient was persistently in the 100 to 150 IU/liter range. Two of 21 nonpsychotic but severely disturbed hospitalized psychiatric patients had increased serum CPK activity. The levels in both patients were modest (> 150 IU/liter). The increases in one of these patients were present intermittently throughout hospitalization and appeared to be a consequence of his "enzyme lability," a tendency to develop markedly increased enzyme activity following exercise of any type.[7] That the grandfather and uncle of this patient were chronically schizophrenic could also be related to his increased enzyme levels, as discussed above. In other reports from this laboratory, few chronically schizophrenic patients or neurotic patients have had increased serum CPK or aldolase activity at admission or during hospitalization.[1-3]

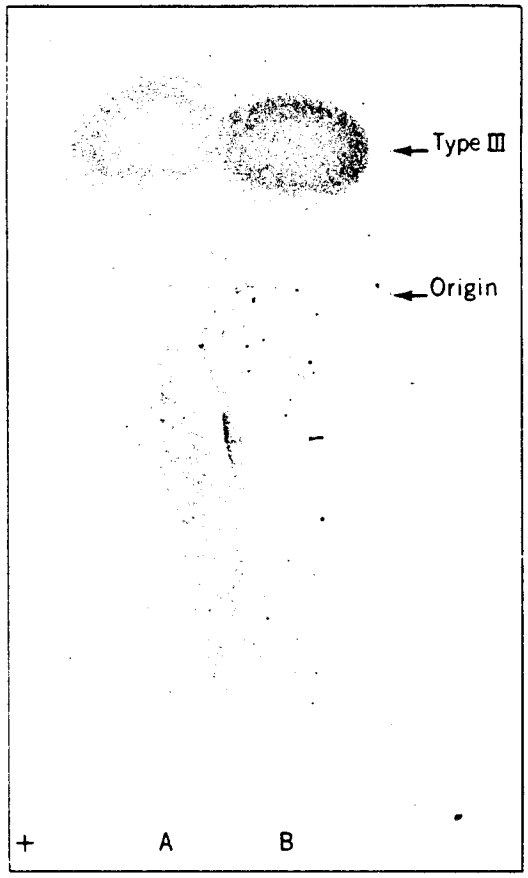

Fig 2.—Creatine phosphokinase isoenzymes of 10,000 g supernatant from muscle homogenate. A, acutely psychotic patient; B, normal control.

Other Serum Enzymes.—In 25 of 43 acutely psychotic patients, the peak serum aldolase activity was greater than the 95% upper confidence limit (3.2 milliunits/ml for women and 2.7 milliunits/ml for men). The median aldolase activity in those patients with abnormal aldolase activity was 4.5 milliunits/ml. Fifteen nonpsychotic hospitalized psychiatric patients had normal serum aldolase activity.

Since the isotropic (type I) band of the myofibril appeared abnormal in approximately one third of the biopsies of acutely psychotic patients,[15] and aldolase is localized in this region of the muscle cell,[33] it seemed of interest to explore whether serum levels of other enzymes localized in this part of the muscle were increased. LDH and PHI

Table 6.—*Creatine and Creatinine Excretion in Psychiatric Patients*

Patients	Mean No. Determinations per Subject	Mean Creatine Excretion (mg/24 hr)*	Mean Creatinine Excretion (mg/24 hr)*	Creatine:Creatinine Ratio*
Acutely psychotic, Male (No.=4)	7	16.4 (5.6)†	1,389 (419)†	1.2 (0.2)†
Nonpsychotic, Male (No.=6)	6	15.9 (13.2)†	1,101 (457)†	1.3 (0.9)†
Acutely psychotic, Female (No.=9)	7	60.1 (60.1)†	980 (132)†	5.7 (5.2)*†
Nonpsychotic, Female (No.=4)	5	50.8 (29.1)†	8,876 (85)†	5.2 (3.8)†

* Numbers in parentheses are standard deviations.
† Not significantly different from nonpsychotic patients of same sex ($P > 0.05$).

are so localized,[33-34] but were rarely or never increased in the sera of the acutely psychotic patients. As discussed by Rowland et al,[35] with reference to Duchenne dystrophy, the failure to find a wide range of muscle enzyme proteins in pathologically abnormal sera from patients with myopathy is more likely to represent a greater rate of clearance from serum of the absent enzyme proteins than a lack of release through binding of the enzyme protein or selective permeability of the cell membrane.

Very slight increases in GOT activity were found in nine of 50 pathologically abnormal sera from acutely psychotic patients. Increased activity of ICDH, MDH, GlDH, and α-HBDH were rarely or never observed in pathologically abnormal sera from acutely psychotic patients although they are frequently increased in patients with Duchenne dystrophy or various liver diseases.[36] Thus, the activities of CPK and aldolase are the only enzymes yet found which are frequently, but not always, increased in the sera of acutely psychotic patients.[1-3]

Muscle Biopsies.—There were no significant differences in the activities of CPK per milligram of protein or per gram of tissue in the total homogenate, mitochondrial pellet, or supernatant from the acutely psychotic patients and the control group (Table 5). Although some of the acutely psychotic patients were receiving chlorpromazine or thioridazine at the time of the biopsy, chlorpromazine does not alter rat muscle CPK activity in vivo or in vitro.[6] Since the total CPK activity of skeletal muscle is many thousand times greater than that of sera and is constantly being replenished by synthesis of new enzyme, it is not surprising that no changes were found.

Agar gel electrophoretic studies of the supernatant fraction revealed only the type III (skeletal muscle) CPK isoenzyme in both the acutely psychotic and nonpsychotic patients (Fig 2). No type I (brain) or type II (cardiac muscle) CPK isoenzymes were detected. Although type II CPK has been found in normal skeletal muscle by some investigators,[37] we were not able to confirm this in muscle biopsy specimens obtained at surgery.

The glycogen content of the muscle of the acutely psychotic patients (No. = 11) was 1.1 gm/100 cc ± SE 0.1 gm/100 cc, not significantly different from the levels in nonpsychotic psychiatric patients (No. = 8), 1.0 gm/100 cc ± SE 0.1 gm/100 cc. Both values are normal.[38]

Creatine-Creatinine Excretion.—The mean 24-hour excretion of creatine and the ratio of creatine to creatinine of the male and female acutely psychotic patients with increased CPK activity were not significantly different from nonpsychotic patients studied simultaneously or from published normal values[30,39] (Table 6). There was a tendency towards greater creatinuria during times when serum CPK activity was increased but not enough such specimens could be collected to evaluate the possibility that creatinuria, like serum CPK activity, might be transiently increased. This possibility will need further investigation. It is clear, however, that no persistent creatinuria occurs in most acutely psychotic patients.

Conclusions

Serum CPK or aldolase activity, or both, were increased in approximately 70% of this sample of acutely psychotic patients of a

variety of diagnostic types. Two separate assays of CPK activity as well as an electrophoretic technique whose sensitivity is such that it cannot detect CPK activity in serum unless the enzyme levels are substantially increased indicated increased amounts of this enzyme.

As in previous reports, the increased CPK levels were generally transient. But, it is of considerable interest that for eight of the patients increased CPK levels were present for periods up to at least 13 months, and have not yet returned to normal levels. Four of the seven acutely psychotic patients with persistent increases in serum CPK activity received chlorpromazine orally in doses of 200 to 400 mg/day; the one chronically ill patient received 1,200 mg of chlorpromazine per day. We have not noted any relationship between orally administered phenothiazines and increased CPK activity previously.[1,2] We have studied many patients receiving prolonged phenothiazine treatment who do not have increased CPK activity. Some subjects, however, respond to intramuscularly administered chlorpromazine with increased serum CPK activity.[6] This has been attributed to a toxic effect of chlorpromazine on muscle.[6] It is possible that in some subjects oral administration can lead to toxic levels of chlorpromazine in muscle. But in the subjects who no longer were receiving phenothiazines, it is not possible to attribute the prolonged increase in CPK activity to drugs. The increased CPK activity in these subjects is in the same range as that found in the carriers of Duchenne-type muscular dystrophy.[12] The increased enzyme activity in the carriers of Duchenne-type dystrophy has been attributed to slightly increased leakage of enzyme from mildly myopathic fibers.[12] A similar explanation is likely for the psychotic patients.

Evidence has been presented elsewhere that 34 of 55 (62%) of the acutely psychotic patients reported on here have morphologic evidence of myopathy[14,15] and that 10 of 22 (45%) have an exaggerated increase in serum enzyme activity following a standardized exercise test in comparison with normal controls.[7] The absence of creatinuria, a normal subcellular distribution and isoenzyme-type of CPK in the muscle of acutely psychotic patients, no clinically detectable muscular weakness in these patients, and normal electromyograms performed on two psychotic patients with abnormal biopsies and elevated serum CPK (H. Meltzer, unpublished data) all indicate that any myopathy which may be present is subclinical. These latter parameters of muscle physiology are generally abnormal only in advanced disease of muscle.

The increased activity of CPK and aldolase in serum,[1-3] which is sometimes persistent, the magnitude of the increases in activity of CPK in serum following exercise,[7] and the histochemical[13-14] and light and electron microscopic abnormalities[15] in muscle biopsies from acutely psychotic patients suggest that a myopathy is present in most patients from the whole spectrum of the so-called functional psychoses. It is premature to interpret the significance of the occasional chronically psychotic, borderline psychotic, or neurotic patient who manifests some or all of the criteria for myopathy present in the acutely psychotic patients. It appears that the myopathic changes we have demonstrated do define, with biological parameters, a relatively unique subgroup of psychiatric patients.

If a myopathy, however subtle, is present in the acutely psychotic patients, this lends support to the hypothesis that an organic disturbance of the central nervous system is present in acutely psychotic patients as well. It seems unreasonable that muscle pathological abnormalities could be present in acutely psychotic patients, which correlate with psychotic symptomatology and sleep disturbance[2,9,40] without neuropathological abnormalities, functional or structural, also being present. No particular implication about the cause of the myopathy or central nervous system disorder follows, however. The abnormalities of muscle could be secondary to the brain disorder or, perhaps, represent independent muscle disease. It is highly unlikely that muscle disease of the type reported here or increased serum CPK and aldolase levels are causally involved in the etiology of psychosis.[3] Schizophrenia and Duchenne muscular dystrophy have been observed in at least one individual,[41] but no association between these disorders has been reported in the many clinical reviews of muscular dystrophy. Patients and

families of patients with myotonia congenita, however, are reported to have a high incidence of psychosis.[42] Increased muscle tension, abnormalities in neuromuscular transmission, and defects in proprioception secondary to abnormalities in muscle spindles have been implicated in the development of schizophrenic symptomatology (reviewed by Lang and Buss[43]).

Abnormalities of the nervous system and muscle are found together in a number of situations. Atrophy of muscle secondary to lower motor neuron or spinal cord disorder is well-known.[44] Less well-appreciated is the fact that central lesions, generally of the parietal lobe, may cause contralateral muscle atrophy.[45] The probability of central nervous system pathological abnormality along with muscle pathological abnormality in Duchenne-type muscular dystrophy has been proposed by many investigators because of the high incidence of mental retardation in this disease.[46-48] The demonstration of neuropathological abnormality in muscular dystrophy is, however, more controversial.[41,49,50] Fenichel has discussed a variety of ways in which brain damage in utero may adversely affect muscle development.[51] Munsat et al[52] have discussed the role of the central nervous system in the etiology of centronuclear myopathy, a rare form of myopathy in which all five cases reported to date have some functional, but not structural, central nervous system disturbance. Their suggestion that "the CNS defect in centronuclear myopathy may be primary with muscle changes reflecting disordered central control" may be relevant for the further study of the myopathic changes in acute psychosis. Furthermore, patients with a variety of acute brain diseases have been reported to have increased serum CPK activity of the muscle-type.[53]

Although the etiology of the myopathy in acutely psychotic patients is unclear, there are many provocative possibilities which can be explored experimentally. We have previously advanced the hypotheses that toxic substances which affect brain and muscle or disturbances in the trophic effect of brain on muscle may be important in the etiology of the serum enzyme changes in acutely psychotic patients.[1-3] Studies in our laboratory have indicated that stress-induced effects on central thermoregulatory centers, with or without changes in body temperature, should be considered as a possible cause of increased serum CPK activity,[54] especially since hypothermia and abnormalities in heat production or loss have been frequently observed in some schizophrenic patients, albeit more chronically ill ones.[55-57] The general parallelism between the psychotomimetic and hyperthermic properties of LSD and its derivatives in rabbits has been known for some time[58] as has the capacity of the phenothiazines to affect central thermoregulatory centers.[59]

Any of the mechanisms suggested as possible causes of increased serum CPK activity in psychotic patients could be based, in part, on a genetic defect, the presence of which is suggested by the increased serum CPK activity in the relatives of acutely psychotic patients and by recent studies on the transmission of schizophrenia.[60] For example, other recent studies have established a relationship between an inherited defect in heat production or loss under general anesthesia and an inherited myopathy.[61,62] Afflicted individuals, prior to administration of general anesthesia, have increased serum CPK activity and show evidence of subclinical muscle disease by physical examination and electromyography. Under a variety of general anesthetic agents with or without muscle relaxants, these people develop severe hyperpyrexia and further breakdown of muscle with massive increases in serum CPK activity.[62] In-so-far as this condition represents an inherited abnormality of muscle and possibly the temperature regulating mechanisms of the central nervous system as well, it may be analogous to one of the possible mechanisms which account for the myopathy in some psychotic patients.

Summary

The activities of creatine phosphokinase (CPK) and other enzymes were monitored in the serum of acutely psychotic patients, their relatives, chronically psychotic patients, and neurotic patients as part of a comprehensive search for evidence of myopathy in acutely psychotic patients. Increased activity of CPK was found in 44 of 64 acutely psychotic patients of all diagnostic

types and in 31 of 75 parents or siblings of these patients. Seven of the acutely psychotic patients had persistently increased activity of CPK. Increased aldolase and aspartate aminotransferase activities were found in 25 of 43 and 9 of 50 acutely psychotic patients respectively. No increases in the activity of serum lactic dehydrogenase, phosphohexose isomerase, malic dehydrogenase, glutamic dehydrogenase, and isocitric dehydrogenase were observed. Increased activity of serum CPK was found in one of 8 chronic schizophrenic patients and in two of 22 nonpsychotic psychiatric patients. Total CPK activity, subcellular distribution of CPK isoenzyme type of CPK, and total glycogen were normal in muscle biopsy specimens from acutely psychotic patients. No creatinuria was present. Morphologic evidence of myopathy and the increase of serum CPK activity following exercise is presented in companion papers[14,15] as additional evidence of muscle abnormalities in acutely psychotic patients.

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Nonproprietary and Trade Names of Drug

Thioridazine—*Mellaril.*

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