neuromuscular dysfunction in schizophrenia*

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During the last 7 years, there have been a number of investigations of the incidence of various types of neuromuscular dysfunction in patients with schizophrenic and affective illnesses and their first-degree relatives in comparison with appropriate controls, including nonpsychotic psychiatric patients. Before reviewing these studies, it may be of value to discuss why neuromuscular dysfunction might be expected in virtually any disease of the nervous system—a category in which, thanks to recent genetic studies, we may now confidently include schizophrenia and the primary affective illnesses. The evidence for central nervous system involvement in a variety of diseases with apparently primary skeletal muscle involvement will also be presented.

There are numerous instances of known disease of the brain in which pathologic changes in lower motor neurons, with consequent effects on skeletal muscle fiber morphology and function, are found. “Central atrophy” is the name given to the atrophy of skeletal muscle fibers, which frequently develops after various chronic brain diseases, particularly tumors of the parietal lobe (Fenichel, Daroff, and Glaser 1964, Koinov and Markov 1971, and Van Crevel 1969). Depth electrode studies in chronic schizophrenics have demonstrated abnormal electrical discharges in various parts of the cerebral cortex, including the parietal lobe (see Mirsky 1969). The mechanism of central atrophy is believed to be loss of the trophic (nutrient) influence of the upper motor neuron on the lower motor neuron (see Guth 1968 for discussion of trophism). In turn, the lower motor neuron is believed to produce and release trophic substances on which skeletal muscle fibers are dependent, such that loss of these trophic factors leads to muscle fiber atrophy (Mendell and Engel 1971). Parkinson’s disease is associated with skeletal muscle atrophy (Edström 1970) perhaps because of the loss of trophic influences or because of muscle rigidity. A small number of pathological muscle fibers of diverse morphology develop in rats after lesions of the substantia nigra or cuts under the globus pallidus (Kanner and Meltzer 1974). Changes in muscle fiber types also develop in monkeys following lesions of the primary or secondary sensory cortical areas (Schwartzman and Dimancescu 1974). Vitamin deficiencies such as pernicious anemia (subacute combined degeneration) can produce brain, motor neuron, and skeletal muscle fiber abnormalities (Brain 1955). Interestingly, mental disturbances may occur in pernicious anemia. These may include paranoia or severe affective illness (McAlpine 1929). There are several disorders of tryptophan metabolism, including pellagra, carcinoidosis, maple syrup disease, and Hartnup disease, in which both mental and neuromuscular symptoms and pathologic findings are present (Lehmann 1972), apparently due to an inadequate amount of tryptophan or its metabolites.

Diseases such as Duchenne-type muscular dystrophy, myotonic muscular dystrophy, myasthenia gravis, and malignant hyperpyrexia are believed by some to be primarily diseases of the nervous system with secondary changes in skeletal muscle fibers (Engel 1971, Konishi et
al. 1974, LaCour, Juul-Jensen, and Reske-Nielsen 1971, McComas, Campbell, and Sica 1971, McComas, Sica, and Brown 1971, and McComas, Sica, and Upton 1974), but this is not generally accepted. Nevertheless, it is important to recall the undisputed high incidence of mental retardation in Duchenne muscular dystrophy (Prosser, Murphy, and Thompson 1969 and Zellweger and Niedermeyer 1965), the dilated ventricles and cerebral atrophy associated with myotonic dystrophy (Refsum et al. 1967), and the oft-noted occurrence of psychosis in families with myotonia congenita (Johnson 1967). "Central core" and fibers with rod bodies are striking pathologic changes in skeletal muscle that appear to be nonspecific in that they do not define a disease entity. There is considerable evidence that these may be due to abnormalities of motor nerves (Dahl and Klutzow 1974, Dubowitz and Roy 1970, Engel 1966, and Karpati, Carpenter, and Andermann 1971). Munsat, Thompson, and Coleman (1969) have discussed the role of the central nervous system in the etiology of centronuclear myopathy, a rare form of myopathy in which functional but not morphological pathology has been identified. They postulated that "the CNS [central nervous system] defect in centronuclear myopathy may, therefore, be primary with muscle changes reflecting disordered central control" (p. 130). Fenichel (1967) has discussed a variety of ways in which brain damage in utero may adversely affect muscle development.

Brune (1971) has called attention to older literature that details the occurrence of cases of simultaneous muscle disease and major mental illness, including a family with three siblings for whom Duchenne-type muscular dystrophy and schizophrenia were said to become clinically manifest at the same time. Although some type of psychopathology may frequently be found in chronic muscle diseases, it is rare that frank psychosis is present (Brune 1971). Beckett and Bourne (1973) summarized evidence that monkeys reared in isolation, a condition known to produce markedly disturbed behavior, had extensive myopathic changes in skeletal muscle, including the diaphragm. Although they rightly concluded that it was impossible to decide if these changes were due to physical inactivity or psychosomatic factors, it would seem that the diaphragmatic changes would argue against simple inactivity as the explanation.

Several skeletal muscle enzymes—for example, creatine phosphokinase (CPK) and aldolase—have a relatively slow disappearance rate from serum so that they may be elevated in serum in a variety of diseases associated with skeletal muscle fiber breakdown. Although the increases are greatest in Duchenne-type muscular dystrophy, elevations also occur in diseases of the lower motor neuron such as amyotrophic lateral sclerosis (Achari and Anderson 1974) and various childhood degenerative diseases of lower motor neurons (Heyck and Laudahm 1967). A variety of known acute brain diseases are associated with elevated muscle-type serum CPK levels; this includes acute cerebrovascular accidents, encephalitis, meningitis, and brain trauma (Dubo et al. 1967 and Eisen and Sherwin 1968). Small increases in serum CPK activity have been found in rats 4 hours after electrolytic lesions of the anterior hypothalamus but not in 13 other brain areas (K. T. Finnegam, H. Y. Meltzer, and M. Kanner, unpublished data).

There is also electrophysiological evidence of abnormalities of lower motor neurons and the skeletal muscle fibers they innervate in patients with a variety of brain diseases. McComas et al. (1973) have found a decrease in the number of viable motor units in patients, beginning 6-12 months after cerebral vascular accidents. Similarly, patients with Parkinson's disease have decreased numbers of functioning motor units (Sica et al. 1973).

Current theories of the nature of the biologic factors that contribute to the pathogenesis of schizophrenia center around abnormalities of bioamines such as the catecholamines and serotonin. There is also considerable evidence that bioamines such as serotonin and adrenaline can produce pathological changes in skeletal muscle (Highman, Altland, and Garbus 1965, Meltzer and Margulies 1971, O'Steen, Barnard, and Yates 1967, and Parker and Mendell 1974). Adrenaline has been reported to have unique effects on the muscle contraction of denervated muscles (Bowman and Raper 1965 and Evans and Smith 1973), which may be relevant to schizophrenics for whom there is evidence of muscle denervation (see below). Similar effects of adrenaline were noted on the muscle of subjects with various muscular dystrophies, suggesting alteration in neurotrophic influence on skeletal muscle in these diseases (Takamori 1975).

Dopamine has been shown to inhibit skeletal muscle contraction by a direct effect on muscle (Blum 1969 and Ferko and Calesnick 1971), which can be inhibited by
cholinergic and haloperidol, suggesting there is a
dopamine receptor in muscle (Capetola, Ferko, and
Calesnick 1974). Dopamine may also have a prejunctional
facilitatory effect on neuromuscular transmission
(Gallagher and Karczmar 1973). Further, either chronic
administration of amphetamine (H. Meltzer, unpublished
data) or phencyclidine plus restraint stress (Meltzer
1972b) can produce skeletal muscle pathology in labora-
tory animals. This effect has been briefly reviewed
elsewhere in this issue (Meltzer and Stahl 1976, p. 00).
Amphetamine and phencyclidine, both drugs capable of
producing psychoses in man that are comparable in some
respects to schizophrenia (Angrist et al. 1974 and Luby
et al. 1962), are well known to have marked effects on
bioamines, which are believed to mediate the mental
changes these agents produce (Hitzemann, Loh, and
Monoamine oxidase (MAO) inhibitors such as pargyline
can produce skeletal muscle damage in rats (Yu et
al. 1974). Thus the finding of decreased MAO activity in
the blood platelets of some schizophrenic and depressed
patients (Wyatt and Murphy 1975) raises the possibility
that decreased MAO activity could be a factor in muscle
abnormalities in psychotic patients. This possibility is
currently being studied in our laboratory by determining
the MAO activity in the skeletal muscle of schizophrenic
patients and controls.

Thus, there are morphological, biochemical, and
electrophysiological indications of neuromuscular dys-
function in patients with a variety of brain diseases, as
well as examples of diseases of lower motor neurons that
can produce skeletal muscle pathology. In addition,
neurotransmitters, which may be relevant to schizo-
phrenia and the pathogenesis of psychotomimetic drug
effects, may produce skeletal muscle toxicity. We will
now review some of the evidence for neuromuscular
dysfunction in schizophrenia.

**Serum Creatine Phosphokinase Activity
in Acute Psychosis**

Demonstration of increased activity of serum en-
zymes associated with skeletal muscle disease—that is,
CPK, aldolase, or pyruvate kinase (PK)—is the most
convenient way available, other than history and physi-
cal examination, to demonstrate the possible presence of
skeletal muscle abnormalities. As will be discussed,
elevated serum CPK, aldolase, or PK activities may result
from causes other than significant muscle disease (Nevins
et al. 1973). These factors must be considered before
increases in serum enzyme activity are attributed to
muscle disease. Once these factors have been taken into
account, determination of serum CPK activity can be a
most sensitive index of skeletal muscle disease. For
example, in those vulnerable to malignant hyperpyrexia,
serum CPK is moderately elevated, sometimes without
any detectable muscle changes on physical examination
(Denborough et al. 1970).1

Serum CPK elevations in acutely disturbed schizo-
phrenics have now been found in 17 studies (table 1),
but the percentage of patients with elevations varies
from 8 to 100 (median = 40 percent). Increased serum
CPK activity has also been reported in other types of
psychiatric patients, especially those with affective
psychoses (table 1). Before discussing the reasons for the
large variations in the incidence of increased serum CPK
activity in acutely disturbed schizophrenics in various
studies, it is useful to review briefly the origin of serum
CPK in psychotic patients and the possible causes of
increased serum CPK activity in psychotic patients that
are not specific to psychosis.

**Origin of Serum CPK Activity**

There are three major isoenzymes of CPK: a brain
type (BB), a skeletal muscle type (MM), and a cardiac
muscle type (MB). Each type is a dimer made up of
some combination of B and M subunits. Brain and
skeletal muscle have almost exclusively BB- and MM-type
CPK, respectively; cardiac muscle has a mixture of all
1Certain general anesthetics (e.g., fluothane, halothane) and
muscle relaxants (e.g., succinylcholine) can evoke massive CPK
increases in individuals who are susceptible to malignant hyper-
pyrexia (Britt 1972). Abundant microscopic pathology is present
in the skeletal muscle of individuals susceptible to malignant
hyperpyrexia, because of an inherent nerve or muscle abnormal-
ity or both (Harriman, Sumner, and Ellis 1973, Issacs, Frere, and
Mitchell 1973, and LaCOUR, JUUL-JENSEN, and Reske-Nielsen
1971). WINGARD (1974) has presented evidence for stress and
excessive sympathetic nervous system reactivity as factors that
contribute to malignant hyperpyrexia. There is a closely related
disease in pigs (soft, exudative pork) in which the trigger for
muscle rigidity, hyperthermia, and massive CPK efflux appears
to be stress (Jones et al. 1972). Meltzer (1973a) called attention
to similarities between malignant hyperthermia and the rare
"lethal catatonia" syndrome reported in schizophrenia. There is
no evidence as yet for the occurrence of major mental illness in
the families of patients with malignant hyperpyrexia.
Table 1. Serum creatine phosphokinase activity in psychiatric patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. elevated/ no. studied</th>
<th>Percent</th>
<th>Recent onset</th>
<th>Schizophrenics</th>
<th>Other psychiatric patients</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schievone and Kaldor (1965)</td>
<td>9/24</td>
<td>37</td>
<td>?</td>
<td></td>
<td></td>
<td>Those with elevation &quot;clinically distinguishable from those without&quot;</td>
</tr>
<tr>
<td>Bengzon, Hippius, and Kanig (1966)</td>
<td>30/60</td>
<td>50</td>
<td>Yes</td>
<td>None</td>
<td></td>
<td>Largest increase in agitated patients, but increase also present in those with normal activity</td>
</tr>
<tr>
<td>Meltzer (1968)</td>
<td>10/12</td>
<td>83</td>
<td>Yes</td>
<td>Excluded</td>
<td>Manic depressive</td>
<td>Increase at admission in 5/18, Increase later in 10/18. Muscle type CPK identified for first time</td>
</tr>
<tr>
<td>Meltzer (1969)</td>
<td>2/11</td>
<td>18</td>
<td>No</td>
<td>Excluded</td>
<td>Psychotic depressive</td>
<td></td>
</tr>
<tr>
<td>Warnock and Ellman (1969)</td>
<td>2/22</td>
<td>9</td>
<td>?</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Meltzer, Elkun, and Molina (1969)</td>
<td>10/22</td>
<td>46</td>
<td>Yes</td>
<td>Excluded</td>
<td>Affective psychosis</td>
<td>Survey of newly admitted patients, eliminating all who had received IM injection. Psychotic patients without increase included six with symptoms less than 6 days</td>
</tr>
<tr>
<td></td>
<td>18/94</td>
<td>19</td>
<td>No</td>
<td>Excluded</td>
<td>Nonpsychotic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute brain syndromes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute CNS disease</td>
<td></td>
</tr>
<tr>
<td>Coffey, Heath, and Guschwan (1970)</td>
<td>14/32</td>
<td>44</td>
<td>?</td>
<td>IM in three patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/42</td>
<td>5</td>
<td>No</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meltzer, Grinspoon, and Shader (1970)</td>
<td>21/39</td>
<td>54</td>
<td>Yes</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meltzer and Molina (1970a)</td>
<td>36/59</td>
<td>72</td>
<td>Yes</td>
<td>None</td>
<td>Manic depressed</td>
<td>Some acute patients without increase also had recent onset of symptoms. Increase preceded psychotic symptoms in a few cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Psychotic depression</td>
<td></td>
</tr>
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</table>
Table 1. Serum creatine phosphokinase activity in psychiatric patients—Continued.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
<th>Schizophrenics</th>
<th>Other psychiatric patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. elevated/ no. studied</td>
<td>Percent</td>
</tr>
<tr>
<td>Meltzer, Nankin, and Rafferty (1971)</td>
<td>Acute (schizophrenics and affectives)</td>
<td>83/209</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Chronic (schizophrenics and affectives)</td>
<td>16/137</td>
<td>12</td>
</tr>
<tr>
<td>Gosling et al. (1972)</td>
<td>4/6 paranoid</td>
<td>4/6</td>
<td>67</td>
</tr>
<tr>
<td>Gosling, Kerry, and Cowen (1972)</td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Schweid, Steinberg, and Sudak (1972)</td>
<td>Psychotic (type not specified)</td>
<td>19/35</td>
<td>54</td>
</tr>
<tr>
<td>Tropeano et al. (1972)</td>
<td>Various types of schizophrenia</td>
<td>19/24</td>
<td>76</td>
</tr>
<tr>
<td>Guterman (1973)</td>
<td>Paranoid schizophrenia</td>
<td>8/18</td>
<td>44</td>
</tr>
<tr>
<td>Loebel and Robins (1973)</td>
<td>Not specified</td>
<td>2/5</td>
<td>40</td>
</tr>
<tr>
<td>Foster and Kupfer (1973)</td>
<td>Acute</td>
<td>3/3</td>
<td>100</td>
</tr>
<tr>
<td>Cunningham et al. (1974)</td>
<td>Diagnosis not specified in either group</td>
<td>7/86</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2/77</td>
<td>3</td>
</tr>
</tbody>
</table>

Comment: First study was of consecutive admissions. No distinction between psychotic and nonpsychotic. IM injections given and patients dropped from study. Questionable normal limit. Second study was of all patients in hospital on a given day.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Patients</th>
<th>Age (Years)</th>
<th>Gender</th>
<th>Excluded</th>
<th>Psychosis Type</th>
<th>Excluded Limit</th>
<th>Excluded Due to Mental Status</th>
<th>LSD Increase</th>
<th>LSD Psychosis</th>
<th>LSD Nonpsychosis</th>
<th>Attribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuason, Oleshansky,</td>
<td>Acute</td>
<td>1/9</td>
<td>11</td>
<td>?</td>
<td>Excluded</td>
<td>Affective psychosis</td>
<td>0/9</td>
<td>No</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Used limits</td>
</tr>
<tr>
<td>and Jarawan (1974)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Undiagnosed</td>
<td>0/5</td>
<td>No</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Owen and Kerry (1974)</td>
<td>Acute</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>Affective disorder</td>
<td>10/10</td>
<td>100</td>
<td>?</td>
<td>No</td>
<td>No</td>
<td>Only increase</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td></td>
<td></td>
<td>0/20</td>
<td>0</td>
<td>No</td>
<td>1/26</td>
<td>4</td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Harding (1974a)</td>
<td>Acute</td>
<td>5/23</td>
<td>22</td>
<td>&lt;1</td>
<td>Excluded</td>
<td>Affective (7) or paranoid (4)</td>
<td>1/11</td>
<td>9</td>
<td>&lt;1</td>
<td>No</td>
<td>No</td>
<td>Attributed</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>0/20</td>
<td>0</td>
<td>No</td>
<td>Excluded</td>
<td>Nonpsychotic</td>
<td>1/26</td>
<td>4</td>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Harding (1974b)</td>
<td>Acute</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>LSD psychoses</td>
<td>4/4</td>
<td>100</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Attributed</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>LSD—nonpsychotic</td>
<td>3/3</td>
<td>100</td>
<td>Yes</td>
<td>1/3</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Meltzer (1976)</td>
<td>Acute</td>
<td>97/123</td>
<td>79</td>
<td>Variable</td>
<td>Excluded</td>
<td>Mania</td>
<td>9/12</td>
<td>75</td>
<td>Yes</td>
<td>Excluded</td>
<td>Excluded</td>
<td>See text</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>62/123</td>
<td>50</td>
<td>Variable</td>
<td>Excluded</td>
<td>Psychotic depression</td>
<td>8/12</td>
<td>67</td>
<td>Yes</td>
<td>Excluded</td>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>28/40</td>
<td>70</td>
<td>Variable</td>
<td>Excluded</td>
<td>Nonpsychotic (anytime increase)</td>
<td>1/19</td>
<td>5</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

1 IM = intramuscular.
2 A second group of patients under the continuous care of other clinicians but whose blood samples were studied by the Gosling group.
three types (Burger, Richterich, and Aebi 1964 and Van der Veen and Willebrands 1966). Other organs have only small amounts of CPK and generally do not contribute to any increase in serum CPK activity. The isoenzymes of CPK can be identified by chromatographic, electrophoretic, or radioimmunologic methods. The CPK in the serum of schizophrenics has been identified as the skeletal muscle type by chromatographic and electrophoretic methods (Meltzer 1969 and Meltzer and Moline 1970a). No brain type was found. This would suggest the origin of the CPK in serum is skeletal muscle, a conclusion that is further supported by finding increased serum aldolase activity (Meltzer 1968 and 1969) and PK activities (G. R. Pschedit and H. Y. Meltzer, unpublished data) in psychotic patients with increased serum CPK activity. Like increased CPK, elevated aldolase and PK levels in serum are associated with skeletal muscle disease (Harano et al. 1973 and Sibley and Fleisher 1959).

If the serum CPK in psychotic patients had its origin in the brain, one might expect increased CPK activity in cerebrospinal fluid (CSF). Such an elevation has been searched for and not found in several studies (Martin, Garey, and Heath 1972, Meltzer 1970 and 1973a, and Meltzer and Moline 1970a). There is, however, one report of increased CSF CPK levels in acute schizophrenics (Vale et al. 1974) and another of increases in patients with LSD psychoses (Votolina 1970). Further study of this problem with sensitive methods of determination of CPK activity or protein and with careful attention to potential artifacts is needed.

Although it may seem that the evidence just reviewed indicates that the origin of the serum CPK in psychotic patients is skeletal muscle, some doubt as to the correctness of this conclusion was introduced by a report that brain-type CPK is unstable in serum, especially in vivo, with rapid conversion to the cardiac and skeletal muscle types (Frotscher et al. 1973). This report has been partially confirmed in our laboratory (Cho et al. 1976). Human-brain-type CPK was found to be unstable in vitro; after incubation for 42 hours, it was found to migrate like the cardiac type, but no skeletal-muscle-type CPK was present. However, in vivo, it is possible that a CPK species that migrates like skeletal-muscle-type CPK could be produced from brain-type CPK.

Somer et al. (1975) have reported very small amounts of brain-type CPK in serum of 8 out of 12 patients with severe brain injuries. At most, brain-type CPK was 23 percent of the total serum CPK, which was mainly the skeletal muscle type. None of the brain-type CPK was detectable more than 12 hours after the severe brain injury; nor was any brain-type CPK detectable in serum in seven patients following neurosurgical operations. This negative finding again documents the transient nature of the presence of brain-type CPK in serum. Assuming brain-type CPK would be as transient in acutely psychotic patients, one can quickly see the difficulty of demonstrating it in psychotic patients who are extremely difficult to study within hours of the onset of psychosis—if indeed onset can even be identified so precisely. The possibility exists that the brain-type CPK is transformed in serum to a species that, though electrophoretically distinct from normal brain-type CPK, is immunologically identical. We are investigating such possibilities. Clearly, studies of the CPK isoenzymes in patients with acute schizophrenic symptoms of a few hours' duration should be pursued. Demonstration of brain-type CPK in these patients would strongly argue for designating those schizophrenic patients as instances of acute brain disease.

Factors Not Related to Psychosis as Possible Causes of Elevated Serum CPK

Intramuscular injections may elevate serum CPK activity. Thus, although less than 50 percent of patients given intramuscular Thorazine have an increase in serum CPK levels following injection (Meltzer, Mrozak, and Boyer 1970), all patients who have received such injections should be excluded in studies attempting to use serum CPK levels for diagnostic purposes. In order not to eliminate the majority of psychotic patients whose serum CPK it would be of interest to determine, intramuscular injections should therefore be avoided; if parenteral medication is needed, subcutaneous prolixin enanthate or intravenous haloperidol might be used, as neither elevate serum CPK (H. Y. Meltzer, unpublished data). Oral psychotropic medication does not influence serum CPK levels in man (Meltzer 1969).

Alcoholism (Nygren 1966) and muscle trauma may increase serum CPK activity and must be excluded by history, laboratory, and physical examination. We have recently found that simulation by volunteers of the type of behavior that psychotic patients sometimes manifest when their limbs are temporarily restrained may lead to
large increases in serum CPK activity that can persist for up to 72 hours (D. J. Goode, D. H. Weinberg, and H. Y. Meltzer, unpublished data). All serum CPK increases that first occur following such restraint must be considered suspect. Dietary factors, including starvation (Balmer and Rutishaure 1968), have not been found to increase serum CPK activity.

Stress does not usually increase serum CPK activity in people without psychotic disorders. Nonpsychotic psychiatric patients experiencing severe anxiety, agitation, or depressive symptoms do not have increased serum CPK levels (Meltzer 1968, 1973b, and 1975). Similarly, preoperative patients generally have normal serum CPK activity (Bennett and Betts 1967). However, we have found moderate increases in serum CPK levels in some psychotic patients before hospital discharge and in several volunteers before administration of psychotomimetic drugs, findings which may be related to stress (Meltzer et al. 1972 and Meltzer and Moline 1970a).

Physical activity is a well-known cause of increased serum CPK activity (Griffiths 1966); but very severe activity (e.g., crew racing and marathon running) is generally required to produce increases, except in a small group of so-called "enzyme-labile" subjects who have large increases in serum CPK activity with relatively slight motor activity (Griffiths 1966). A variety of indirect evidence summarized elsewhere suggests increased motor activity is not a sufficient explanation of the increased serum CPK levels in most psychotic patients (Meltzer and Moline 1970b). We have recently found that the increases in serum CPK levels produced in psychiatric patients by exhausting isometric exercise do not exceed those present during other phases of hospitalization (Goode and Meltzer, in press). Although Foster and Kupfer (1973) reported that serum CPK levels during certain periods of the day and nondominant arm motor activity monitored by telemetry were correlated, and although we have found that nurses' ratings of motor activity and CPK activity are significantly correlated (Meltzer 1975), such correlations do not prove causality. Motor activity and serum CPK activity, in some patients, could both be the consequence of a basic neurochemical abnormality in psychosis—for example, increased dopaminergic activity.

Sleep disturbance in psychotic patients, particularly non-rapid-eye-movement sleep time, is correlated with serum CPK levels (Meltzer et al. 1970) and may be another example of a central nervous system function that correlates with serum CPK levels without requiring a causal relationship. In normal volunteers, sleep deprivation for 48 hours can produce modest increases in serum CPK activity (Kupfer et al. 1970).

Magnitude and Duration of Increased Serum CPK Activity in Psychotic Patients

Normal limits of serum CPK activity vary for the four black and white race-sex groups (Meltzer 1971 and Meltzer and Holy 1974). Most clinical laboratories employ either one broad range for all subjects or at most have separate limits for males and females. Blacks have significantly higher serum CPK levels than whites, probably on a genetic basis (Meltzer and Holy 1974), and any study of serum CPK activity in psychiatric populations with blacks should employ the appropriate limits. Cunningham et al. (1974) reported few increases in a population of newly admitted psychiatric patients but used only one broad range of normality for all four race-sex groups. If the normal limits were adequate for black males, then they must have been too high for all other race-sex groups.

The increases in serum CPK activity in psychotic patients vary from just above the upper limit of normal for each race-sex group to up to 220 times the upper limit, but the median increase is two to three times the 95-percent upper limits (Meltzer 1975 and Schweid, Steinberg, and Sudak 1972).

The duration of the serum CPK increases in psychotic patients is highly variable; in some instances, it is slightly elevated beyond normal limits for just a day. In other patients, levels may be moderately elevated for a month or even longer, but for 75 percent of patients the duration of the increase is 1-7 days (Meltzer 1975). The very brief, modest elevations (less than twice normal) may, in fact, be normal fluctuations in response to activity or minor trauma. Even these small increases, however, generally do not occur in nonpsychotic psychiatric patients studied as intensively as psychotic patients (Foster and Kupfer 1973, Gosling et al. 1972a, Meltzer 1969 and 1975, Meltzer, Elkin, and Moline 1969, and Schweid et al. 1972), but have been reported by Tropeano et al. (1972) and Loebel and Robins (1973). Increases present at admission may be followed by normal serum CPK throughout hospitalization or a later period of increased serum CPK activity (Meltzer 1975). In some instances, the increases are present only later in
hospitalization (Meltzer 1969 and 1975) and generally occur during an intensification of psychotic symptoms. Of the 23 studies of serum CPK activity in psychiatric patients (table 1), only Meltzer (1968, 1969, and 1975), Meltzer, Grinspoon, and Shader (1970), Meltzer and Moline (1970b), and Foster and Kupfer (1973) measured serum CPK activity throughout hospitalization. Obviously, continuous measurement increases the possibility of identifying more of the increases that may occur.

**Clinical Characteristics of Psychiatric Patients With and Without Increased Serum CPK Activity.**

Meltzer (1975) has established that the incidence of serum CPK elevations in patients in whom the onset of psychotic symptoms occurred less than 1 week before admission is significantly greater than in those with onset more than 1 week before admission. Thus, if the florid phase of a psychotic episode began more than 1 week before admission and if serum CPK elevation began within a few days of the onset of that episode and lasted only 1-7 days, serum CPK activity might well be normal at admission. Only a few studies of serum CPK activity have considered onset of psychotic symptoms as a variable (table 1), and none of those which found less than 10 percent of psychotic patients with increases did (Cunningham et al. 1974 and Tuason, Oleshansky, and Jaranson 1974). Since increases in serum CPK activity are present in myocardial infarction for no more than 2-3 days (Konttinen and Halonen 1963), many false negatives would occur if there were a delay in obtaining blood samples in this condition.

Some psychiatric patients with prolonged periods of psychotic symptoms before admission nevertheless have increased serum CPK at admission, while there are patients with psychotic symptoms of only a few days' duration who do not show increases (Meltzer 1969 and 1975 and Meltzer and Moline 1970a). It is important, therefore, to determine why some but not all recent-onset acutely psychotic patients have increased serum CPK activity.

Guterman (1973) evaluated schizophrenic patients with the Brief Psychiatric Rating Scale (Overall and Gorham 1962) and found significant correlations between increased serum CPK activity and increased motor activity, total psychopathology, thought disturbance, and withdrawal-retardation. Gosling et al. (1972) evaluated psychotic patients with the Inpatient Multidimensional Psychiatric Scale (IMPS) (Lorr and Klett 1966 and Lorr et al. 1962) and found that increased serum CPK activity was most likely to be present in manic patients with high ratings on the IMPS second-order factor, disorganized hyperactivity, and in paranoid schizophrenic patients with high ratings on the IMPS second-order factors, paranoid process and hostile paranoia. Meltzer (1973a) noted no differences in these second-order IMPS factor scores in the schizophrenic population originally studied by Meltzer, Grinspoon, and Shader (1970).

As we have discussed elsewhere in this issue of the Bulletin (Meltzer 1976, see p. 10), the most effective way to identify the sources of the variance in a biochemical parameter in schizophrenics may be to collect a large body of developmental, behavioral, psychological, response to treatment, and family history data in a large group of patients, diagnosed by well-defined criteria, and relate these data to the biological parameter by appropriate statistical analyses. We have been engaged in such a study with regard to increased serum CPK activity. Only the preliminary results have been reported so far (Meltzer 1975) and will be summarized here.

Increased serum CPK activity was present in 88 out of 187 (47.1 percent) of all psychotic patients at admission (table 2). Serum CPK levels in all patients were subsequently studied Monday through Friday throughout hospitalization. By discharge a total of 142 of the 187 psychotic patients (75.9 percent) had had an increase beyond 95-percent limits. This incidence was similar for patients with 1) acute schizophrenia, paranoid and nonparanoid types; 2) chronic schizophrenia, paranoid type; and 3) psychotic depression (unipolar and bipolar depressions of psychotic proportions). Chronic schizophrenics, nonparanoid type, and manic-depressive patients, manic phase, had a somewhat lower percentage of increases in serum CPK activity at admission, but both categories of patients had larger percentages of patients with late increases (increases that occurred for the first time late in hospitalization) so that when the entire hospitalization was considered, all types of psychotic patients had about equal percentages of increases (67-82 percent). It is important to point out that the patients considered chronic in this study were for the most part experiencing a major exacerbation of
psychotic symptoms after a period of relative remission outside the hospital. Chronically hospitalized schizophrenic patients with dormant symptomatology would not be expected to have increased serum CPK activity. In all categories of psychotic patients, a larger percentage of the total group had additional periods of increased serum CPK activity following admission (table 2). The incidence of these late increases was not significantly different in those with or without increases at admission. We are currently studying the relationship of these late increases to psychopathology, stress, trauma, and physical activity.

The incidence of increased serum CPK levels in good prognosis and poor prognosis schizophrenic patients as determined by the Stephens-Astrup Scale (Stephens, Astrup, and Mangrum 1966) was not significantly different—89 out of 113 (79 percent) vs. 36 out of 50 (72 percent) (Meltzer 1975).

Psychotic patients with increased serum CPK at admission had higher peak ratings of five of eight nonredundant items of a 14-item daily behavior rating scale administered during the 1st week of hospitalization than psychotic patients without such increases. The rating scale is derived from Hargreaves (1968) and has been described elsewhere (Meltzer 1975). The significantly different items between psychotic patients with and without increased serum CPK activity included ratings of psychotic behavior, paranoia, lack of effective contact with staff and patients, hyperactivity, and anger. There were no significant differences in ratings of depression, underactivity, and anxiety.

A discriminant function analysis of ratings for all 14 items of the daily rating scale found that peak admission ratings significantly discriminated between patients with and without increased serum CPK activity (H. Y. Meltzer, G. Lucht, and P. A. Holy, unpublished data). Psychotic patients with increased serum CPK levels had higher ratings on psychiatric illness (a measure of global psychopathology) and anxious manner. This analysis statistically controlled for differences in the time of onset of psychotic symptoms between the two groups.

It would appear that those patients with increased serum CPK activity at admission, or later in hospitalization, tend to have a more florid psychosis that is relatively more treatment resistant for the episode. The psychotic patients without serum CPK increases tend to be of two types: acutely ill patients with brief, treatment-responsive illnesses, and chronic patients, who are admitted after only relatively slight intensification of their psychosis. There have been exceptions to the generalizations. Some markedly disturbed, very recent onset psychotic patients have not had increased serum CPK levels, either at admission or anytime. The explanation for these exceptions may depend, in part, on such factors as variations in basic control mechanisms for serum CPK regulation as described in the next section. It may also be, however, that heterogeneity of the schizophrenia syndrome contributes to the differences.
Serum CPK Activity in Nonpsychotic Periods as a Factor in Serum CPK Elevations

We were interested in investigating the possibility that psychotic patients who had an elevation in serum CPK levels beyond the 95-percent upper limits of normal for each race-sex group at any time during hospitalization also had higher serum CPK levels at other times during hospitalization than those psychotic patients who never had such increases. We therefore determined a mean serum CPK activity for each psychotic patient using all samples obtained during hospitalization except those that exceeded the 95-percent upper limits of normal, all samples for 5 days after a muscle biopsy, and all samples 3 days after an intramuscular injection. As can be seen in tables 3 and 4, mean serum CPK levels were significantly greater for all psychotics with an elevation in serum CPK activity at any time during hospitalization than for those psychotics who never had such an increase. Similar results were obtained when the highest serum CPK level during the last 2 days of hospitalization was used for each psychotic patient (Meltzer 1975). These findings suggest the possibility that a more sustained increase in skeletal muscle permeability or a slower rate of enzyme clearance from plasma could contribute to the tendency to have a period of serum CPK activity greater than the upper limits of normal. It suggests the possibility of a biochemical diathesis that could contribute to the development of an increase in serum CPK activity during a psychotic exacerbation.

Serum CPK Levels in First-Degree Relatives of Psychotic Patients

A significant proportion of first-degree relatives of both schizophrenic patients and patients with affective psychoses have serum CPK levels that are near to or slightly exceed the 95-percent upper limit of normal (Meltzer 1973b and 1975 and Meltzer and Moline 1970a). Of 314 first-degree relatives of 134 psychotic patients, 101 (32.2 percent) had elevated serum CPK levels based on the 95-percent norm for their respective race-sex groups (Meltzer 1975). The increases are present in approximately the same percentage of parents, siblings, and children of psychotic patients. Studies are in progress to determine if a significant relationship between serum CPK levels in these relatives and the index patients is present. The findings in first-degree relatives

Table 3. Mean serum CPK levels for all psychotic patients with elevated serum CPK at any time versus no elevation by sex-race groups.

<table>
<thead>
<tr>
<th>Race and sex</th>
<th>Increase at any time</th>
<th>No increase in serum CPK activity at any time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>M</td>
</tr>
<tr>
<td>Black males</td>
<td>36</td>
<td>69.1</td>
</tr>
<tr>
<td>White males</td>
<td>29</td>
<td>43.5</td>
</tr>
<tr>
<td>Black females</td>
<td>59</td>
<td>40.6</td>
</tr>
<tr>
<td>White females</td>
<td>33</td>
<td>27.6</td>
</tr>
</tbody>
</table>

Table 4. Analysis of variance results for mean CPK.

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex/race</td>
<td>3</td>
<td>6776.920</td>
<td>20.787</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Increase/no increase</td>
<td>1</td>
<td>8650.093</td>
<td>26.501</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Interaction</td>
<td>3</td>
<td>567.871</td>
<td>1.742</td>
<td>—</td>
</tr>
<tr>
<td>Within</td>
<td>204</td>
<td>326.024</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
take on added significance in that serum CPK levels have been found to be under significant genetic controls based on studies of normal (Meltzer et al., in press a) and schizophrenic monozygotic and dizygotic twins (H. Y. Meltzer, E. Dorus, R. Belmaker, L. Grunus, and J. M. Davis, unpublished data). Heritability indices for serum CPK activity of 0.6-0.8 have been found in these studies.

**Serum CPK Activity in Acute Brain Diseases**

Increased serum CPK activity has been reported in patients with hemorrhagic and thrombotic cerebrovascular disease, necrotic gliomas, cerebral anoxia, status epilepticus, brain trauma (e.g., gunshot wounds), subarachnoid hemorrhages, drug-induced coma, encephalitis, and meningitis (Acheson et al. 1965, Dubo et al. 1967, and Eisen and Sherwin 1968). The characteristics of the serum CPK increases in acute brain syndromes and the acute psychoses are similar to each other and distinctly different from those in chronic neurogenic muscle disease or a myopathy such as polymyositis (table 5).

Although there are basic similarities in the time course and magnitude of the serum CPK increases in psychotic patients with well-defined acute brain diseases, these similarities do not mean the increases all have the same etiology. Among the possible causes of muscle enzyme release that might obtain during an acute organic brain disease are disruption of tonic or phasic upper motor neuron influences on lower motor neurons, loss of trophic substances transported to muscle via blood or nerve, elaboration of myotoxic substances by the brain or other organs, and changes in muscle blood flow, muscle electrolyte composition, oxygen supply, or muscle contraction patterns and intensity. Any one factor or any combination thereof might be operative in the acute psychoses and acute brain syndromes. As previously mentioned, the possibility of release of CPK from brain in both the acute psychoses and acute brain diseases must be considered.

**Significance of Serum CPK Studies in Schizophrenia**

The determination of the significance of elevated serum CPK in schizophrenia must await definitive evidence that it is not an artifact in a good proportion of cases. At present, this evidence is circumstantial and will remain so until the pathophysiology is understood. Clearly, demonstration that the CPK in serum is coming from brain rather than muscle would greatly enhance its significance. Although this possibility must certainly be pursued, it seems a remote one to the author. The increases may be useful for diagnostic purposes. Unless care is taken regarding alcoholism, trauma, and intramuscular injections as causes of increases, however, there will be false positives; similarly, there will be many newly admitted schizophrenics who will have normal serum CPK activity. Nevertheless, as the first readily available biochemical method for identifying at least some psychotic patients, this test may be of some merit: the first small step in using a laboratory approach to diagnosis in psychiatry. In an early investigation (Meltzer and Moline 1970a) and in that of Gosling et al. (1972), it was claimed that increased serum CPK activity sometimes occurred before the onset of gross psychotic symptoms; in our more extensive studies, we have not been impressed with this as a frequent occurrence. Pursuing the possibility of slightly elevated serum CPK levels in first-degree relatives of psychotic patients may be of value for theoretical and genetic purposes.

### Table 5. Comparison of increased serum CPK activity in acute psychoses, acute brain diseases, polymyositis, and chronic neuromuscular diseases.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Time after onset of 1st CPK increase</th>
<th>Time from onset of increase to peak increase</th>
<th>Duration of CPK increase</th>
<th>Magnitude of CPK increase</th>
<th>Percent of patients with CPK increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute psychoses</td>
<td>1-3 days</td>
<td>1-3 days</td>
<td>1-7 days</td>
<td>$1^+ - 2^+$</td>
<td>50</td>
</tr>
<tr>
<td>Acute brain diseases</td>
<td>1-3 days</td>
<td>1-3 days</td>
<td>1-7 days</td>
<td>$1^+ - 2^+$</td>
<td>60</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>1 day</td>
<td>Variable</td>
<td>Variable</td>
<td>$1^- - 4^+$</td>
<td>80</td>
</tr>
<tr>
<td>Chronic neuromuscular</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Prolonged</td>
<td>$1^- - 2^+$</td>
<td>60</td>
</tr>
</tbody>
</table>
major values of the serum CPK studies may be heuristic: They have prompted the search for other parameters of neuromuscular dysfunction in psychotic patients.

Skeletal Muscle Fiber Abnormalities in Psychotic Patients

If increased serum CPK levels are not due to such factors as increased physical activity, intramuscular injections, or trauma, they are frequently the result of diseased skeletal muscle fibers, which can be demonstrated morphologically. This finding prompted us to examine skeletal muscle specimens from psychotic patients, their first-degree relatives, nonpsychotic psychiatric patients, and normal controls. The methods and earlier results of our studies have been presented in detail elsewhere (Fischman, Meltzer, and Poppei 1970, Meltzer 1972a, Meltzer, McBride, and Poppei 1973, Meltzer and Crayton 1974 and 1975, and Meltzer and Engel 1970). Our current studies will be briefly summarized here.

Careful quantitative methods are critical for the study of skeletal muscle morphology in psychotic patients. In only about 10 percent of the 300 muscle specimens examined from psychotic patients are the pathological changes in muscle fibers so marked that they would be definitely considered abnormal by clinical pathologists who generally use very broad, relatively undefined limits of normality to avoid false-positive diagnoses. This approach is the correct one for ordinary purposes because only extensive pathological changes in muscle have any functional consequences. As an index of the possible presence of a subtle pathologic process in muscle and possibly motor nerves, however, quantitative norms derived from appropriate controls are not only clearly superior but absolutely necessary. We obtained, therefore, 16 quadriceps and 18 peroneus brevis muscle specimens from control subjects without personal or family history of psychiatric or neuromuscular illness. The criteria derived from the controls for abnormality of the peroneus brevis muscle, the muscle we now biopsy in psychotic patients, are presented in detail elsewhere (Meltzer et al., in press b, and Meltzer, Rastogi, and Ellison, in press) and are summarized in tables 6 and 7. There is slightly less pathology in the vastus lateralis. In comparison with increased central nuclei, atrophic fibers and extensive Z-streaming (Z-streaming occupying portions of at least three continuous sarcomeres and three adjacent fibrils), which were the most common forms of pathology in normals, type grouping, ring fibers, early necrotic fibers, and splitting fibers were even rarer. No fibers undergoing phagocytosis, alkaline phosphatase positive-fibers, fibers with nemaline rods, target fibers, targetoid fibers, or fibers with cytoplasmic masses were observed in the normal controls.

The percentages of the more common types of muscle abnormalities in the various groups of subjects are given in table 8. They are illustrated in figures 1-3. The most common histochemical abnormality in psychotic patients was excessive numbers of scattered atrophic fibers that were present in 32.5 percent of all psychotic patients. This abnormality was present in similar percentages of schizophrenics and patients with affective psychoses. The other histochemical abnormalities were

Table 6. Incidence and number of abnormal fibers per 1,000 in peroneus brevis specimens from normal volunteers.

<table>
<thead>
<tr>
<th>Item</th>
<th>Incidence</th>
<th>Range</th>
<th>M</th>
<th>SD</th>
<th>95% confidence limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nuclei</td>
<td>13/16</td>
<td>0-20.4</td>
<td>5.4</td>
<td>5.6</td>
<td>17.6</td>
</tr>
<tr>
<td>Small round fibers</td>
<td>12/16</td>
<td>0-3.5</td>
<td>1.3</td>
<td>.95</td>
<td>2.7</td>
</tr>
<tr>
<td>Small angular fibers</td>
<td>9/16</td>
<td>0-5.4</td>
<td>1.2</td>
<td>1.7</td>
<td>4.9</td>
</tr>
<tr>
<td>Angular fibers</td>
<td>7/16</td>
<td>0-3.6</td>
<td>.67</td>
<td>.95</td>
<td>2.7</td>
</tr>
<tr>
<td>All atrophic fibers (2+3+4)</td>
<td>15/16</td>
<td>0-10.2</td>
<td>3.1</td>
<td>2.6</td>
<td>8.8</td>
</tr>
</tbody>
</table>
Table 7. Extensive Z-band streaming in normal human skeletal muscle.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Incidence</th>
<th>Fibers with extensive Z-streaming (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
</tr>
<tr>
<td>Male</td>
<td>5/14</td>
<td>36</td>
</tr>
<tr>
<td>Female</td>
<td>3/4</td>
<td>75</td>
</tr>
<tr>
<td>Combined</td>
<td>8/18</td>
<td>44</td>
</tr>
</tbody>
</table>

Table 8. Percentage of patients and controls with specific muscle abnormalities.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Scattered atrophy</th>
<th>AP$^+$ fibers</th>
<th>Central nuclei</th>
<th>Necrotic fibers</th>
<th>Splitting fibers</th>
<th>Ring fibers</th>
<th>Extensive Z-streaming</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>34</td>
<td>8.8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonpsychotics</td>
<td>19</td>
<td>5.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5.3</td>
</tr>
<tr>
<td>All psychotics</td>
<td>166</td>
<td>32.5</td>
<td>9.0</td>
<td>7.2</td>
<td>7.8</td>
<td>7.2</td>
<td>4.2</td>
<td>19.9</td>
</tr>
<tr>
<td>Acute schizophrenics</td>
<td>108</td>
<td>29.6</td>
<td>12.0</td>
<td>4.6</td>
<td>7.4</td>
<td>1.9</td>
<td>2.3</td>
<td>19.4</td>
</tr>
<tr>
<td>Chronic schizophrenics</td>
<td>36</td>
<td>38.9</td>
<td>5.6</td>
<td>13.8</td>
<td>8.3</td>
<td>16.7</td>
<td>5.6</td>
<td>16.7</td>
</tr>
<tr>
<td>Bipolar, manic phase</td>
<td>12</td>
<td>33.3</td>
<td>0</td>
<td>33.3</td>
<td>8.3</td>
<td>16.7</td>
<td>0</td>
<td>25.0</td>
</tr>
<tr>
<td>Psychotic depression</td>
<td>10</td>
<td>40.0</td>
<td>0</td>
<td>10.0</td>
<td>10.0</td>
<td>20.0</td>
<td>20.0</td>
<td>30.0</td>
</tr>
<tr>
<td>First-degree relatives of psychotics</td>
<td>26</td>
<td>34.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>23.1</td>
</tr>
</tbody>
</table>

$^1$ AP$^+$ = alkaline phosphatase-positive fibers.

Present in less than 1 to 9 percent of the psychotic patients. These include alkaline phosphatase-positive fibers, excessive central nuclei, necrotic fibers, splitting fibers, ring fibers, fibers with rod bodies, targetoid fibers, fibers with abnormalities of the intermyofibrillar network, atrophic fascicles, and fiber-type atrophy. The incidence of most of these abnormalities in all psychotic patients was sufficiently rare that only excessive atrophic fibers and Z-streaming were present significantly more commonly in the psychotic patients than in the 34 volunteers. The overall incidence of biopsies that were abnormal by any histochemical or phase criteria in the normal volunteers, nonpsychotic psychiatric patients, psychotic patients classified according to diagnosis, and first-degree relatives of psychotic patients is given in table 9. Five of the 34 specimens from controls were sufficiently deviant from one criterion of normality to be considered abnormal, as was one specimen from the 19 nonpsychotic patients. There was no statistically significant difference in the incidence of abnormal specimens between these two groups. The finding that 115 of 166 psychotic patients (69.3 percent) had abnormal muscle specimens was significantly different from that for controls ($\chi^2 = 42.17, p < .001$). All of the major psychoses were associated with similar incidences of abnormal biopsies. There was a tendency, however, for the incidence of abnormal muscle specimens in chronic schizophrenic patients (30 out of 36, 83 percent) to be slightly greater, although not significantly so, than that in the combined group of patients with remitting psychoses (the acute schizophrenics and the patients with affective psychoses) of whom 85 out of 130 (65.4 percent) had abnormal skeletal muscle ($\chi^2 = 3.47, p < .10$).

Thirteen of 26 first-degree relatives of psychotic patients had an excess number of abnormal skeletal muscle fibers—an incidence that was significantly greater than that found in the controls ($\chi^2 = 7.14, p < .001$).
and not significantly less than that found in the psychotic patients ($\chi^2 = 2.94$, $p < 0.10$). Two of the three relatives with the most abnormal biopsies were hospitalized for nonpsychotic psychiatric illnesses. One was diagnosed borderline and the second, neurotic depression. The other relative with a very abnormal
biopsy compared to the rest of the group was the son of two manic-depressives. He has experienced moderate depressions and periodic mood swings, but has not sought psychiatric treatment. This finding illustrates the importance of considering the family history when using nonpsychotic psychiatric patients as controls.

The percentage of muscle specimens that were abnormal by histochemical or phase criteria, or both, is given in Table 10. It is apparent that the histochemical abnormalities were more common than the phase abnormalities and that the overall incidence for the various groups of psychotic patients did not differ appreciably except that the psychotically depressed patients had a higher incidence of abnormal muscle specimens by histochemical criteria. Only about one in five specimens from psychotic patients were abnormal by both histochemical and phase criteria.

The percentage of fibers characterized by the types of abnormalities discussed above varied widely. For example, we considered some biopsies abnormal because they had just one alkaline phosphatase-positive fiber. One specimen from a manic-depressive patient, however, had 34 percent type I fibers, nearly all of which had central cores (Meltzer 1972a), while a specimen from a schizophrenic patient had rods in nearly 40 percent of the fibers (Meltzer, McBride, and Poppei 1973). The 95-percent upper limit of normal for atrophic fibers in the peroneus brevis muscle was 12.9 per 1,000. The number of scattered atrophic fibers in the peroneus brevis muscle of the psychotic patients ranged from 14 to 58 per 1,000. The percentages of muscle specimens that had extensive Z-band streaming for the various diagnostic groups are given in Table 10. The percentage of patients with extensive Z-streaming was about the same in all types of psychotic patients. The percentage of muscle fibers in a given specimen with extensive Z-streaming varied from 2.5 to 31.5 percent. Other abnormalities present in Araldite-embedded muscle specimens such as rods, central core fibers, and necrosis were even rarer. No evidence of glycogen or lipid accumulation was noted.

We found no relationship between increased serum CPK activity at any time during hospitalization and the presence of a muscle specimen abnormal by any criteria. The percentage of abnormal muscle specimens was not significantly different in the entire group of psychotic patients with and without increased serum CPK activity (Meltzer and Crayton 1975). This is not altogether surprising since the increases in serum CPK activity are phasic events that are not usually present when the biopsies are performed. The muscle fibers that account for increased serum CPK activity could have normal morphology at all times, let alone at the time of biopsy. It is also important to recall the possibility that the CPK in the serum of psychotics comes from brain, not muscle.

No relationship was found between maximum dose of medication or total dose of medication (either neuroleptic, tricyclic antidepressants, or lithium carbonate) and the incidence or extent of muscle abnormalities in psychotic patients (Meltzer and Crayton 1975). The first-degree relatives of psychotic patients who had abnormal biopsies had not been treated with psychotropic medication. Rats given up to 30 days of chlorpromazine, 10 milligrams per kilogram, intraperitoneally, daily, did not develop any muscle

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Abnormal (percent)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>34</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>Nonpsychotics</td>
<td>19</td>
<td>5.3</td>
<td>ns</td>
</tr>
<tr>
<td>All psychotics</td>
<td>166</td>
<td>69.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Acute schizophrenics</td>
<td>108</td>
<td>69.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chronic schizophrenics</td>
<td>36</td>
<td>83.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bipolar, manic phase</td>
<td>12</td>
<td>66.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Psychotic depression</td>
<td>10</td>
<td>80.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>First-degree relatives of psychotics</td>
<td>26</td>
<td>50.0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Figure 2. Histochemically abnormal skeletal muscle fibers in psychotics—II.¹

¹ Upper left: Type I targetoid fibers indicated by arrows, NADH-TR, X 200. Upper right: Fibers with rod bodies indicated by arrows, trichrome, X 220. Middle left: Arrow indicates rods, X 580. Middle right: Fiber with cytoplasmic bodies, trichrome, X 540. Lower left: Necrotic fiber, trichrome, X 740. Lower right: Alkaline phosphatase-positive fiber, X 870.
Figure 3. Extensive Z-band streaming in skeletal muscle fibers of psychotics.¹

¹ Upper panel: Araldite-embedded muscle with extensive Z-band streaming (ZS), × 500. Middle panel: Araldite-embedded muscle, rod bodies, × 250. Lower panel: Araldite-embedded muscle, targetoid fiber, also known as central core (CC), × 500.
Table 10. Percentage of muscle biopsies abnormal by histochemical, phase, or both criteria in psychiatric patients, first-degree relatives, and controls.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Histochemical abnormal</th>
<th>Phase abnormal</th>
<th>Both abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>34</td>
<td>8.8</td>
<td>5.8</td>
<td>0</td>
</tr>
<tr>
<td>Nonpsychotics</td>
<td>19</td>
<td>5.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All psychotics</td>
<td>166</td>
<td>53.6</td>
<td>34.3</td>
<td>18.7</td>
</tr>
<tr>
<td>Acute schizophrenics</td>
<td>108</td>
<td>50.0</td>
<td>33.3</td>
<td>19.4</td>
</tr>
<tr>
<td>Chronic schizophrenics</td>
<td>36</td>
<td>63.9</td>
<td>36.1</td>
<td>16.7</td>
</tr>
<tr>
<td>Bipolar, manic phase</td>
<td>12</td>
<td>41.7</td>
<td>33.3</td>
<td>8.3</td>
</tr>
<tr>
<td>Psychotic depression</td>
<td>10</td>
<td>70.0</td>
<td>40.0</td>
<td>30.0</td>
</tr>
<tr>
<td>First-degree relatives of psychotics</td>
<td>26</td>
<td>42.2</td>
<td>23.0</td>
<td>15.3</td>
</tr>
</tbody>
</table>

abnormalities (H. Y. Meltzer, unpublished data). That evidence suggests that the muscle fiber abnormalities are not a drug effect. Since the patients were relatively young and had no history or evidence of trauma, diabetes, vitamin deficiency, other serious illnesses, or prolonged inactivity, it is unlikely that any of these factors could account for their presence.

In addition, no relationship was found between abnormal muscle specimens in psychotic patients and 1) age, 2) race, 3) sex, 4) Stephans-Astrup prognosis scores, 5) family history of hospitalized mental illness, 6) total number of psychiatric hospitalizations, or 7) interval between onset of current episode and biopsy.

Subterminal Motor Nerve Abnormalities in Psychotic Patients and Relatives

The primary cause of the various abnormal muscle fibers found in specimens from psychotic patients could be abnormalities of motor nerves rather than intrinsic pathology in the muscle fibers. This interpretation is based, in part, on evidence that the types of pathologic muscle fibers found in the muscle specimens of psychotic patients, especially scattered atrophic fibers, fibers with rods and central cores, fiber-type grouping, and extensive Z-streaming could result from abnormalities of the motor neuron, as could increased serum CPK activity (see Meltzer 1972a for references). To initiate a quantitative investigation of whether any part of the alpha motor neuron was abnormal in psychotic patients, the subterminal motor axon and the subneural apparatus were examined using the supravital staining method of Coers and Woolf (1959) as modified by Evans et al. (1970). If there were degeneration or severe impairment of function of some motor neurons at the level of the nerve cell body, axon, or subterminal region, surviving healthy nerves should branch at the level of the subterminal motor axon in order to reinnervate muscle fibers deprived of their innervations (Cöers and Woolf 1959). Supravital staining permits visualization of such branching as well as other abnormalities of the subterminal motor nerves.

Axonal branching may lead to more than one terminal arborization (nerve ending) on one muscle fiber or in the innervation of more than one muscle fiber. A quantitative expression of axonal branching can be obtained by calculating the terminal innervation ratio (TIR). The absolute TIR (ATIR) is defined as the average number of subterminal motor arborizations per motor axon (Coers and Woolf 1959). The functional TIR (FTIR) is the average number of muscle fibers innervated per subterminal nerve (Coers and Woolf 1959). In normal muscles, no more than 10 percent of subterminal motor nerves branch or innervate more than one muscle fiber. The range of the FTIR in normal controls is 1.01-1.20 (mean = 1.10 plus or minus a standard deviation of .06) (Coers, Teleman-Toppet, and Gérard 1973a). Similar values of the ATIR are found in normals (Coers and Woolf 1959). Meltzer and Crayton (1975) confirmed this in nine normal controls and also found similar results in three nonpsychotic patients. The data from these 12 subjects were pooled to form a comparison group (table 11). Excessive branching and excessive multiple innervation of muscle fibers were
noted in some psychotic patients and in first-degree relatives of psychotic patients (table 11). An example of a subterminal neuron with excessive branching from a psychotic patient is given in figure 4. The mean ATIR and FTIR of all psychotic patients were significantly greater than those of the comparison group. The ATIR and FTIR for all patients and relatives, elevated or not, were virtually identical (data not presented).

The 95-percent upper limit of normal for the ATIR of the comparison group is 1.25; for the FTIR, it is 1.24. The incidence and percentage of specimens that exceed the 95-percent upper limit for the various groups are given in table 12. Forty-four percent of all psychotic patients had increased ATIR's and FTIR's as did 63 percent of the first-degree relatives of psychotic patients. These proportions are not significantly different and reflect a lower percentage of psychotic patients with elevated ATIR's or FTIR's than previously observed in a smaller group of psychotic patients (16 out of 24, 67 percent) (Meltzer and Crayton 1974). The failure to again obtain significant differences may be due in part to the more conservative upper limit of normal (i.e., FTIR greater than 1.25 rather than 1.16). The more conservative limit is based on data from 12 rather than 6 control subjects and a more conservative means of calculating the confidence limit for a single sample (Hays and Winkler 1971). The percentage of psychotic patients with abnormal ATIR's ranged from a low of 35 percent for acute schizophrenics (N = 46) to a high of 80 percent for bipolar, manic-phase patients (N = 5), but not much significance is attributed to this difference because of the small size of the group of manic patients.

In addition to branching, large numbers of sprouts (branches without terminal arborizations) were seen in patients but not controls (Meltzer and Crayton 1974). The terminal arborizations of the psychotic patients also tended to be more fragmented and dispersed than those of the controls.

In a smaller group of these patients for whom data analysis was completed, there was no relationship between age, sex, race, prognosis, the number of psychotic episodes a patient had had, the interval between the onset of the psychotic symptoms of this psychotic episode and the time when the biopsy was performed, or peak dose of phenothiazines and the ATIR or FTIR (Meltzer and Crayton 1974).

There was also no relationship between the presence of elevated serum CPK activity at any time during hospitalization and either an abnormal ATIR or FTIR. Patients whose biopsies were abnormal by either histochemical or phase criteria, however, had significantly higher incidence of elevated ATIR's (29 out of 53) than those whose muscle specimens were normal by both criteria (2 out of 13, $\chi^2 = 5.001, p < .02$). The relationship between the FTIR and abnormal muscle fibers just failed to reach statistical significance ($\chi^2 = 3.565, p < .10$).

Of the 66 psychotic patients for whom there were complete serum-CPK-activity, histochemical, phase, and TIR data, 64 (94 percent) had either increased serum

<table>
<thead>
<tr>
<th>Table 11. Absolute and functional terminal innervation ratios.</th>
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<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Comparison</td>
</tr>
<tr>
<td>Controls of Cöers, Telerman-Toppet, and Gérard (1973a)</td>
</tr>
<tr>
<td>All psychotic patients</td>
</tr>
<tr>
<td>Acute schizophrenics</td>
</tr>
<tr>
<td>Chronic schizophrenics</td>
</tr>
<tr>
<td>Bipolar, manic phase</td>
</tr>
<tr>
<td>Psychotic depression</td>
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<tr>
<td>First-degree relatives</td>
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CPK activity at some time during hospitalization, abnormal skeletal muscle specimens, or significantly elevated TIR's.

The data reported here suggest that some psychotic patients of all common diagnostic types have excessive numbers of abnormal muscle fibers and abnormalities of the subterminal motor nerves. Because of the nature and extent of such pathology and the possibility of non-specific causes, however, interpretation of these findings must be cautious. There were many different types of abnormal muscle fibers observed in the frozen sections and Araldite-embedded muscle specimens. Only excessive numbers of scattered atrophic fibers and a greater than normal percentage of fibers with extensive Z-band streaming were present in nearly 20 percent or more of the specimens from all psychotic patients. The other deviations from normal occurred relatively infrequently over the entire sample: for example, 1-9 percent of patients had alkaline phosphatase-positive fibers, excessive numbers of ring fibers, rod bodies, central core fibers, and other types of pathology previously cited. There were relatively large amounts of pathology in 15 psychotic (9 percent) patients. The extensive pathology was varied: two cases of rod bodies, one of central core fibers, two of alkaline phosphatase-positive fibers, two of fiber-type atrophy, four of scattered atrophic fibers, and four of extensive Z-band streaming. In all the other 102 patients with abnormal muscle specimens by the criteria given here, the amount of a given type of pathology observed in the 34 specimens was actually only slightly to moderately more than in the age-matched controls.

Figure 4. Subterminal motor nerve with excessive branches.¹

¹ Three terminal arborizations on three different muscle fibers, methylene blue, X 360.
Table 12. Incidence of abnormal ATIR's and FTIR's.

<table>
<thead>
<tr>
<th>Group</th>
<th>ATIR</th>
<th>Abnormal (percent)</th>
<th>FTIR</th>
<th>Abnormal (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All psychotics</td>
<td>0/12</td>
<td>0</td>
<td>0/12</td>
<td>0</td>
</tr>
<tr>
<td>Acute schizophrenics</td>
<td>30/68</td>
<td>44</td>
<td>30/68</td>
<td>44</td>
</tr>
<tr>
<td>Chronic schizophrenics</td>
<td>14/40</td>
<td>35</td>
<td>15/40</td>
<td>38</td>
</tr>
<tr>
<td>Bipolar, manic phase</td>
<td>8/15</td>
<td>53</td>
<td>7/15</td>
<td>47</td>
</tr>
<tr>
<td>Psychotic depression</td>
<td>4/5</td>
<td>80</td>
<td>4/5</td>
<td>80</td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>4/8</td>
<td>63</td>
<td>4/8</td>
<td>50</td>
</tr>
</tbody>
</table>

\[ \chi^2 \text{ (ATIR)} = 14.909, p < .02; \chi^2 \text{ (FTIR)} = 13.761, p < .02.\]

An example of this type of specimen would be one with only one alkaline phosphatase-positive fiber. In our controls and in the 100 examined by Engel and Cunningham (1970) and W. K. Engel (personal communication), not one alkaline phosphatase-positive fiber has ever been present in a muscle specimen. By these standards, the patient’s biopsy is abnormal. It is clear that by the criteria of absolute amount of pathology, the muscle specimen from this individual is not impressively abnormal. Nevertheless, there is an apparent continuum of pathology within the entire series that makes it difficult to dismiss the findings of slight pathology as meaningless. The relatively small amount of pathology in the psychotic patients may be due to only selective vulnerability of some motor nerves or muscle fibers or branching of viable subterminal motor nerves to restore innervation to muscles. It is also possible that had we obtained specimens from different muscles or at different times, more extensive pathology might have been present. Extensive autopsy studies might be valuable in this regard. Further study of normal controls and more refined ways of determining abnormalities of muscle fibers and subterminal motor nerves will be needed to determine if there is definite muscle pathology in psychotic patients.

The diversity of muscle pathology in our patient group may not be surprising in light of the relative nonspecificity of muscle pathology. The same pathologic changes in muscle may be found in a multiplicity of diseases, and variation in the type of pathology can frequently be found in different patients with the same disease (Dastur and Razzak 1973 and Engel 1966 and 1967). Therefore, it is hazardous to speculate about common or unique causes for the various pathologic changes found in patients with different types of the major mental illnesses. Nevertheless, all of the types of pathology that we have found in psychotic patients have been attributed by experienced muscle pathologists to abnormalities of the muscle innervation rather than to primary muscle disease (see Meltzer 1972a for references). A similar hypothesis for the etiology of the muscle abnormalities in psychotic patients is attractive because it allows for the possibility of a linkage between the muscle fiber abnormalities and any neuronal abnormalities of the central nervous system that may underlie psychosis.

The multibranched subterminal motor neurons, as illustrated in figure 4, may be the first definitely abnormal neurons or more precisely, parts of neurons, reliably demonstrable in a substantial percentage of psychotic patients. Regardless of whether these prove to be part of the core disease process of the major psychoses, a residue of nonspecific pathologic processes in the life of psychotic patients, or iatrogenic (e.g., the result of antipsychotic medication), they should have considerable significance in the history of research in the major psychoses where the search for abnormal neurons has virtually been without success.

Our current studies suggest that neither medication trauma, age, sex, race, hospitalization, or intercurrent illness can explain the increased branching of subterminal motor neurons in psychotic patients or their first-degree relatives. The excessive branching in the first-degree relatives has particular significance. It is in
agreement with the evidence that the major psychoses have genetic components, and it indicates that this genetic diathesis can express itself prior to the development of florid psychotic symptoms. It of course leaves unclarified why only some people vulnerable to develop psychosis, as indicated by the increased TIR's, become psychotic. The fact that the incidence and magnitude of the elevated TIR's in the first-degree relatives were comparable to those in the index cases suggests but does not prove that the phase of florid psychotic symptoms does not lead to more extensive motor nerve degeneration. (This conclusion is also supported by the lack of a difference in muscle fiber abnormalities and TIR's in patients with just a single psychotic episode and those with multiple attacks.)

Why some, but not all, psychotic patients have abnormalities of the TIR's is not yet understood. Not all the patients with muscle disease, which definitely affects the subterminal nerves, have elevated TIR's (Cöers, Telerman-Toppet, and Gérard 1973). Conceivably, the sampling problem explains some of these inconsistencies: Sampling different areas of the same muscle or other muscles might produce a higher proportion of increases. Whether psychopathological factors or genetic factors are significant, as is the case with elevations in serum CPK activity, remains to be determined.

The chronicity of the motor nerve and muscle fiber pathology would help to explain the lack of correlation between increased serum CPK activity and either of the TIR's or skeletal muscle fiber pathology. The release of CPK from skeletal muscle is greatest during the acute phase of the psychosis and may be the result of transient neurochemical events that are common to a variety of acute brain diseases (Meltzer 1975b).

Branching is a common response of nerve tissue to a variety of toxic and metabolic insults. The key question is what initially promoted the loss of neurons that leads to branching. At the present time, we can only speculate. The pattern of branching in psychotic patients is much more characteristic of a primary neuronal disease than of a primary muscular disease. This conclusion arises from the observation that both the ATIR and FTIR were increased in psychotic patients and they were virtually identical. This pattern occurs when most of the new branches innervate previously denervated muscle fibers rather than increase the number of end plates on already innervated muscle fibers. In primary muscle disease, the death and removal of pathologic muscle fibers usually leads to the FTIR being close to unity (Cöers and Woolf 1959). The most common exception to this rule is in myositis where branching may increase both the ATIR and FTIR (Cöers and Woolf 1959). There were no signs of myositis in the psychotic patients. Thus, the elevation of ATIR's and FTIR's together with a variety of changes in skeletal muscle fiber morphology, which could be neurogenic in etiology, is highly suggestive of the existence of neurogenic muscle disease in some psychotic patients, as was proposed by the author prior to the study of subterminal motor nerves (Meltzer 1972a).

The finding that a significantly greater proportion of muscle specimens characterized by abnormal ATIR's were from patients who had abnormalities of their muscle fibers as well suggests an important relationship between the pathology of the subterminal motor nerves and the muscle fibers. This possibility is underscored by the facts that different aliquots of muscle were used for the determination of the TIR's and the histochemical and the phase microscopic studies, and that all specimens were examined entirely independently.

If, as these data suggest, psychotic patients have an abnormality of motor neurons, a variety of pathophysiological mechanisms could be involved. Possible causes of alpha-motor neuron pathology in the psychotic patients include vitamin deficiency and diabetes mellitus; but since routine laboratory workup and physical examination revealed no evidence of abnormalities consistent with these diseases, it seems highly unlikely that they play a causal role. Nerve compression does not lead to sprouting (Cöers and Woolf 1959). It is possible that the motor nerve abnormalities in some psychotic patients are due to 1) intrinsic alpha-motor neuron pathology like that seen in a variety of degenerative spinal cord diseases such as syringomyelia or Werdnig-Hoffman disease; 2) alpha-motor neuron dysfunction that could be due to some suprasegmental defect—for example, “central atrophy” (Fenichel, Daroff, and Glaser 1964)—or possibly some physiologic process such as increased dopaminergic influence on spinal cord motor neurons; or 3) endogenous substances toxic to alpha-motor neurons. All these possibilities are capable of experimental verification.

The significance, if any, of abnormalities of the motor nerves for motor performance in psychotic patients is an intriguing question. Impaired psychomotor performance in schizophrenics was demonstrated as long
ago as the 1930's (Holzman 1972). Fish and Alpert (1962) have demonstrated abnormalities of skeletal muscle tone and activity in children born of schizophrenic patients. Holzman (1972) has argued that "motor functioning and coordination of various movements is a crucial aspect of the process of organization and control of psychological process" (p. 37). Conceivably the abnormalities of motor nerves reported here might affect a number of critical fine motor processes such as eye movements, larynx, and finger dexterity such that they contribute to psychotic patients' difficulties in adaption. Shimazono et al. (1965), Moriya et al. (1972), Holzman et al. (1974), and Shagass, Amadeo, and Overton (1974) have recently reported abnormalities of eye movements in most schizophrenic and some affectively psychotic patients and their first-degree relatives. These abnormalities might be functional correlates in the eye muscles of the denervation and branching found in the peroneus brevis muscle.

It is of interest to point out that the multibranched subterminal neuron (see figure 4), although abnormal, is an attempt to maintain function, just as a hypertrophied muscle fiber is. While significant branching of the subterminal motor nerves of eye muscles could interfere with fine motor control, this problem is presumably less acute than atrophy of the muscle fibers, which could occur without branching. It is tempting to speculate that excessive neuronal branching might occur to a significant extent in the central nervous system of an individual with schizophrenic or affective psychoses. The extent of disability might depend on what type of new connections were made. It seems improbable that there should be denervation and reinnervation in the peripheral motor nerves of psychotic patients without comparable abnormalities or attempts at restoration of function in the central nervous system.

Neurophysiological Studies of Peripheral Motor Nerves

Preliminary neurophysiological studies have also been carried out by Crayton, Meltzer, and Goode (1975) in relation to serum CPK activity, skeletal muscle fiber pathology, and subterminal motor nerve branching in 44 psychotic patients. The H-reflex recovery curve, which provides an index of alpha-motor nerve excitability, was significantly related to the diagnosis of psychosis and increased serum CPK activity. The H-reflex is a monosynaptic response evoked by submaximal stimulation of a mixed motor and sensory nerve (Magladery and McDougal 1950). The afferent discharge travels in the lower threshold sensory fibers. The H-response, recorded from the appropriate muscle, occurs as a result of discharge of the afferent fibers of the two neuron arc or monosynapse in the spinal cord. When two test stimuli are applied to the mixed nerve at various intervals, the second H-response is modified by residual effects of the first stimulus on the alpha-motor neuron. The ratio of the evoked muscle response following the second stimulus to the response following the first stimulus (H₂/H₁) can be plotted against the delay between stimuli to generate an H-reflex recovery curve. Twenty-one of 35 (60 percent) schizophrenic patients and 4 of 9 (44 percent) patients with affective psychoses had abnormal recovery curves compared to 2 of 20 (10 percent) from a normal control group. The abnormalities in the patients were of two types: 1) delayed onset of initial recovery and a markedly reduced or absent peak of secondary facilitation when the second stimulus was given 100-300 milliseconds (msec) after the first, and 2) an accentuation of the trough following secondary facilitation at 300-500 msec. Both findings suggest decreased excitability of the alpha-motor neuron. Each of nine patients with serum CPK levels that exceeded 300 international units per liter had abnormal recovery curves. It is of interest that increased central nervous system dopaminergic activity can produce decreased alpha-motor excitability (Anden, Jukes, and Lundberg 1964) in view of the possible relevance of increased dopaminergic activity to both schizophrenia and mania (Sack and Goodwin 1974 and Snyder et al. 1974). This finding is but one of the many possible bridges between neuromuscular dysfunction and aminergic theories of the major psychoses.

D. J. Goode and H. Y. Meltzer (unpublished data) have noted significant percentages of schizophrenic patients with decreased nerve conduction velocities, increased distal latencies, and increased muscle activity at rest as detected by surface electrode electromyography. The findings of increased muscle activity at rest support the report of Whatmore and Ellis (1964) who used somewhat different methods. These findings do not appear to be due to medication, although further study is needed.
Conclusion

Measurement of serum CPK activity in psychiatric patients may occasionally be of value for the differential diagnosis of psychotic from nonpsychotic psychiatric patients. But because the duration of any increases is often brief, because those with less florid symptomatology have increases significantly less frequently than the more severely ill psychotic, and because some nonpsychotic patients may have increases caused by injections, trauma, or alcoholism, the main value of determining serum CPK activity for psychiatry may be heuristic. It has already led to studies that have demonstrated a variety of pathologic changes in the neuromuscular system of psychotics, including morphologic changes in muscle fibers and subterminal motor nerves and physiologic abnormalities in nerve conduction velocity and spinal cord reflex mechanisms. Other techniques for investigating the spinal cord, motor nerves, and muscle fibers should be employed in the study of psychotic patients and may yield further information about the extent of involvement of the neuromuscular apparatus in psychosis. Collectively, these studies contribute to the evidence for an organic component of the major psychoses. Perhaps, they will also provide significant insight into the causes of the major psychoses as well. It is possible that the causes of the neuromuscular dysfunction may be related to the causes of the psychoses themselves. Conceivably, determining the causes of the neuromuscular dysfunction can be useful to test current theories of the etiology of the schizophrenic and affective psychoses or to generate new hypotheses.

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