neurons, which he terms "gnostic" cells (*11*). We submit that the "counting" cells described here behave as though they code the abstract property of number and are by definition gnostic cells; however, it is entirely possible that the behavior of "counting" cells is the result of complex prior stimulus processing, perhaps by networks analogous to Hebb's cell assemblies.

The extent to which neural coding of stimuli develops as a result of experience is a fundamental problem, particularly for cells that code complex aspects of stimuli. Hebb (*12*) and Konorski (*11*) agree that complex coding, whether by cell assemblies or gnostic cells, is learned. At the other extreme, it has been suggested that even very complex attributes of stimuli may be coded by single neurons as a result of predetermined structural organization (*13*), as evidenced by Hubel and Wiesel's demonstration that complex coding of visual stimuli by cortical neurons is present in the very young kitten (*14*). Insofar as number coding is concerned, Miller, Galanter, and Pribram suggested that an innate stimulus-characteristic/brain-model comparison mechanism may form the basis of the abstract property of number (*15*). The data shown in Fig. 2 would seem to favor this general view. The cell, a "number 6 or 7" counter, was obtained in the association cortex of an 8-day-old kitten. The counting effect is perhaps less striking here than in the cells obtained in adult animals and does not reach statistical significance ($N = 24$, $D = 0.233$, $P < .2$). Although the modal value does not appear to be completely independent of interstimulus interval, the tendency is still clear.

Studies of concept learning in humans suggest that color, shape, and number may form an ordered series of increasingly complex concepts (*16*). It is perhaps relevant that differential neural coding of color appears to occur at or below the level of the visual thalamus (*17*), that neurons coding shape are found by the level of the visual cortex (*10*), and that number may be coded in association areas of the cortex. However, it must be emphasized that the data presented here merely show that, under the conditions of our experiments, certain cells in the association cortex fulfill the operational requirements necessary to code the concept of number. It remains to be demonstrated that these "counting" cells function to code number of stimulus events in the organism under conditions of normal behavior.

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Histochemical Abnormalities of Skeletal Muscle in Patients with Acute Psychoses

Abstract. *In 29 acutely psychotic patients (mostly schizophrenic), histochemical abnormalities of a myopathic type were demonstrated in skeletal muscle biopsies from 13 and were generally correlated with elevation of the "muscle" type isoenzymes of creatine phosphokinase in the patients' serum. The incidence was much higher than found in normal controls, hospitalized neurotic psychiatric patients, or parents of acutely psychotic patients. A diazo-coupling type of "alkaline phosphatase" reaction was particularly useful in identifying abnormal muscle fibers.*

A rise in the blood of the "muscle" type isozymes of creatine phosphokinase (CPK) associated with acute exacerbations of psychoses of various kinds has been reported (*1*). Histochemical abnormalities of a myopathic type have now been demonstrated in skeletal muscle biopsies from such patients.

Muscle biopsies were obtained from 29 patients with acute exacerbations of psychoses, 22 of whom were schizophrenic, the others having affective, paranoid, or involutional psychoses. They were compared with biopsies from two chronic schizophrenic patients, 11 hospitalized nonpsychotic psychiatric patients, four parents (one also an acute psychotic) of acutely psychotic patients, 45 nonpsychiatric normal control subjects, and 142 nonpsychiatric patients with various neuromuscular diseases. Biopsies averaging 8 by 8 by 12 mm were obtained from the gastrocnemius or vastus lateralis. No patient had any significant trauma, including that caused by needles, to the muscle prior to its being biopsied. The specimens were rapidly frozen within 5 minutes of removal (*2*), and kept well frozen until sections were cut from each specimen. Sections stained with the methods for modified trichrome (*3*), reduced nicotinamide adenine dinucleotide–tetrazolium reductase (NADH-TR) (*4*), myofibrillar adenosine triphosphatase at *p*H 9.4 (*5*), basophilia (thionine), and "alkaline

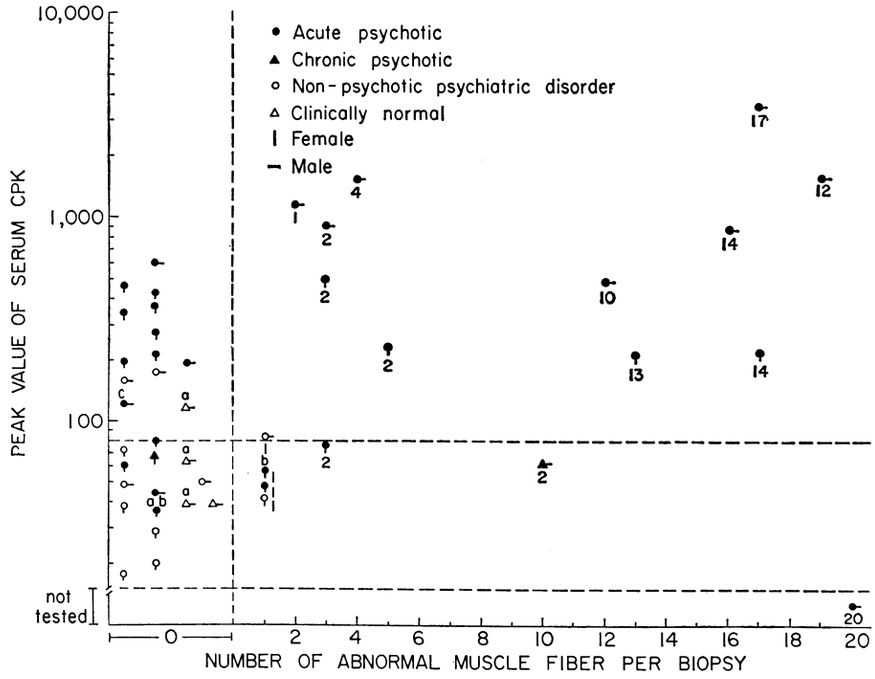

Fig. 1. Muscle biopsy abnormalities correlated with serum CPK values and clinical psychiatric diagnosis. A serum CPK value of more than 80 I.U./liter is abnormal for ambulatory patients. (*a*) Parent of acute psychotic; (*b*) patient seen in remission from acute psychosis, could have had elevated CPK during exacerbation; (*c*) patient had none of the four counted changes, but 25 percent of fibers contained rods. Subscripts: number of alkaline phosphatase–positive fibers within the total abnormal fibers per patient.

phosphatase" (AP) by the α-naphthol phosphate and fast blue RR method at *p*H 8.8 (*6, 7*). Biopsies from 41 of the 42 psychotic and neurotic patients, from four relatives of the acutely psychotic patients, and from one normal control were processed and read by one of us in Bethesda (W.K.E.) without any knowledge of the clinical state or CPK levels which were evaluated by the other (H.M.) in Chicago. At the end of the study the data were collated for possible correlations. The other 187 nonpsychiatric normal and disease controls were part of a larger histochemical evaluation of the "alkaline phosphatase" reaction in neuromuscular disease (*7*).

The number of abnormal muscle fibers per biopsy was recorded (Fig. 1). Abnormalities were of four types: (i) alkaline phosphatase–positive fibers (Fig. 2); (ii) necrotic fibers undergoing phagocytosis demonstrated with the modified trichrome method (Fig. 3); (iii) fibers with a typical moderate architectural and staining abnormality (broadening and irregularity of the intermyofibrillar network seen with the modified trichrome and NADH-TR reactions), with slight to moderate reduction in size and internal nuclei but without phagocytosis (Fig. 4); and (iv) end-stage atrophic necrosis (Fig. 5).

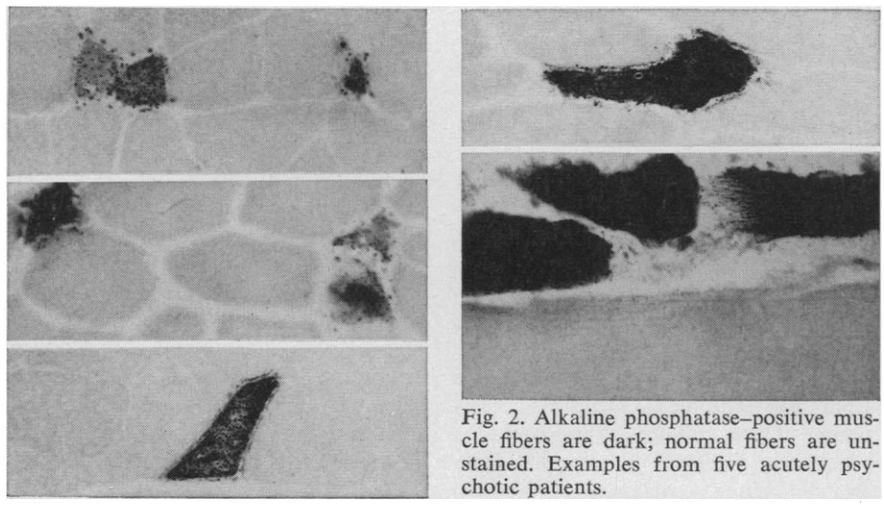

Fig. 2. Alkaline phosphatase–positive muscle fibers are dark; normal fibers are unstained. Examples from five acutely psychotic patients.

On the basis of our histochemical experience with more than 1500 abnormal and normal muscle biopsies from various types of patients, we do not consider the following to be of definite pathologic significance (*8*) and have discounted them in the present study: slight type 2 fiber atrophy, less than 15 striated annulet fibers, cytoplasmic bodies in less than five fibers, rods in less than five fibers, or fewer than five small angular fibers excessively dark with NADPH-TR reaction. (All biopsies contained more than 1500 fibers.)

The muscle biopsy findings (Fig. 1) show (i) 13 of 29 acutely psychotic patients had abnormal biopsies with two or more abnormal fibers (as defined for this study) per biopsy, while another two were borderline (one abnormal fiber). As a corollary, about half (11 out of 21) with CPK levels greater than 80 I.U./liter had abnormal biopsies (an additional acute schizophrenic patient hospitalized at NIH had 20 abnormal fibers, but CPK activity was not studied). (ii) Of the two chronically psychotic patients, one had a normal biopsy and the other, a definitely abnormal one; in both patients CPK activity was essentially normal. (iii) Among the 11 patients with nonpsychotic psychiatric disorders, nine had normal biopsies and two had borderline biopsies (one abnormal fiber); one of the latter two had a slightly elevated CPK. (iv) Three parents of acutely psychotic patients had normal biopsies and CPK's even though one was acutely psychotic herself; one parent of an acutely psychotic manic-depressive patient had mild elevation of CPK and minor morphologic changes consisting of about 5 percent of the fibers with internal nuclei and 40 type 2 fibers with striated annulets. (v) No abnormal fibers were found in the 44 normal control subjects (*7*).

In one acutely psychotic patient (acute paranoia) with slight elevation of CPK (peak of 122 units), more than 25 percent of the muscle fibers contained rod-shaped particles characteristic histochemically (Fig. 6) and electron microscopically (*9*) of rod (nem-

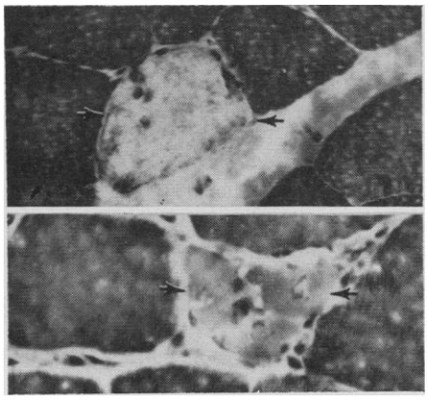

Fig. 3. Muscle fiber undergoing necrosis and phagocytosis. Examples from two acutely psychotic patients; modified trichrome stain.

aline) myopathy (*10*). Because none of the previous patients with rod myopathy was psychotic and because this patient's muscle biopsy had none of the four types of muscle fiber abnormalities mentioned above, the association was tentatively considered fortuitous (since strength was normal, he was considered a subclinical case of rod myopathy). Three other acute psychotics had one fiber each containing several rodlike particles, but this is not necessarily pathologic (*10*).

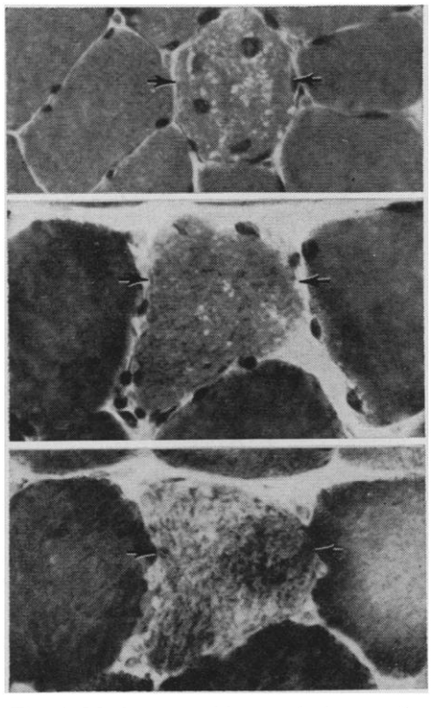

Fig. 4. Moderate architectural abnormality of muscle fiber. Bottom two figures are serial sections. Top two are modified trichrome stain, bottom one is NADPH-TR reductase. Examples from two acutely psychotic patients.

A positive AP reaction is a striking indicator of abnormal muscle fibers in the acutely psychotic patients. Since normal human skeletal muscle fibers are not stained with this reaction (*7*), all AP-positive fibers are considered abnormal. The AP-positive fiber is not undergoing total necrosis with phagocytosis. It is probably undergoing either a milder form of degeneration or a certain stage of regeneration, or both, simultaneously (*7*). Alkaline phosphatase–positive fibers are numerous in active myopathies and sometimes in severe denervation (*11*). Since the biopsies from psychotic patients which contained AP-positive abnormal fibers did not show moderate or severe denervation (and the one with very slight denervation had 14 AP-positive fibers, 13 fibers more than any of the 20 nonpsychotic disease controls with slight denervation) nor severe type 2 fiber atrophy, the abnormal fibers are interpreted as indicative of a mild myopathic process. They are of the same type and distribution as in carriers of Duchenne muscular dystrophy (*7*) but are more prevalent in the acutely psychotic patients in whom they occur.

The other three types of muscle fiber abnormalities recorded are the changes characteristic of the myopathies, including the muscular dystrophies and the various forms of polymyositis. When any or all are the predominant feature of a biopsy they are considered diagnostic of a myopathy (*8*).

There seem to be general correlations between the presence of histochemically abnormal muscle fibers, acute psychosis, and elevated blood CPK (Fig. 1). If these correlations reflect a unified biological phenomenon, two facts could be invoked to explain those acutely psychotic patients who had normal CPK activity or muscle biopsy, or both: (i) muscle biopsy is a small sampling procedure that can miss involved fibers (*2*); and (ii) elevations of blood CPK which occur with acute exacerbations of psychoses are transient (*1*). Furthermore, it is likely that not all acutely psychotic patients have a myopathy; and conceivably the diagnosis of acute psychosis was not always infallible. It may be postulated that the nonpsychotic psychiatric patients with borderline abnormal biopsies may represent intermediate forms of the myopathy and mental disturbance present in the acutely psychotic patients.

There did not appear to be extraneous causes for the muscle fiber histochemical abnormalities in these patients, such as antecedent muscle trauma, other neuromuscular disease or type of drug treatment. Three of the six acutely psychotic patients with ten or more AP-positive fibers had not received phenothiazines prior to the biopsy. More patients must be studied to completely exclude such factors.

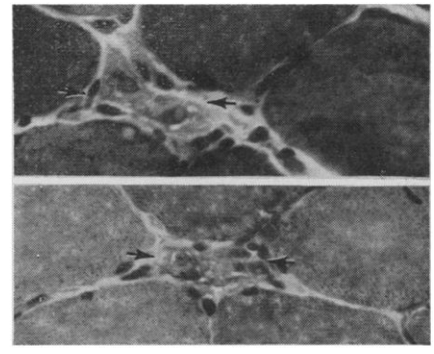

Fig. 5. End-stage atrophic necrosis of muscle fiber. Examples from two acutely psychotic patients; modified trichrome stain.

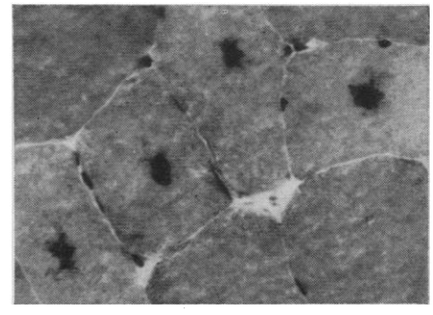

Fig. 6. Clusters of darkly stained rods in the centers of four otherwise normal type 2 muscle fibers. Acutely psychotic patient; modified trichrome stain.

If extraneous factors are not responsible for the histochemical abnormalities in the acutely psychotic patients, the AP-positive fibers represent morphologic evidence of an extracerebral organic disease process in some acutely psychotic patients. It remains to be determined what relationship, if any, these muscle abnormalities have to the mental disturbance in such patients; but their high degree of correlation with acute psychosis supports the possibility of a significant relationship.

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11. It has been shown in human muscle biopsies (*7*) (i) that no AP-positive fibers were present in 43 biopsies from normal subjects or in 37 with various benign neuromuscular disorders (including slight and moderate type 2 muscle fiber atrophy); (ii) that many AP-positive fibers are found in active muscular dystrophies, polymyositis, and moderate and severe denervation atrophy (a small number are found in clinically normal carriers of Duchenne pseudohypertrophic X-linked muscular dystrophy, in which they are a typical lesion); (iii) that rare (two or less) AP-positive fibers occur in certain myopathies with moderate clinical neuromuscular symptoms (of 20 patients with mild denervation four had two AP-positive fibers and others none); five patients with severe type 2 muscle fiber atrophy had up to three AP-positive fibers.

12. We thank Dr. M. Matz and Miss Sarah Burnett for assistance in obtaining the muscle biopsies and G. G. Cunningham for performing the histochemical reactions. Supported in part (H.M.) by grant 17-340 from the State of Illinois and PHS grant 1-RO1-MH-16127 to H.M.

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Alarm Response of Diadema antillarum

Abstract. Diadema antillarum *possesses a sensitive escape response to juices of crushed conspecific sea urchins. Stimulation usually results in urchins moving rapidly downcurrent. Strong species specificity of the response suggests that it is an adaptation to reduce predation.* Diadema antillarum *also responds with a running response to contact with* Cassis tuberosa, *a known predator.*

Swimmers who have blundered into the spines of *Diadema antillarum* know only too well how effectively this Caribbean sea urchin is shielded from harm. The slender barbed spines, sometimes over 30 cm long, are needle-sharp and brittle, readily breaking off in the flesh. As if mere possession of these formidable weapons were not enough, *Diadema* also employs a well-known shadow response when approached: the spines are waved about in a rapid manner which makes it quite difficult to grab a single spine. If one touches a spine the animal immediately brings others to bear on the point of contact. The organism is seemingly invulnerable.

We were surprised, then, to find little piles of *Diadema* spines and skeletal structures in the shallows of the Bimini lagoon in the summer of 1969. Evidently some animal was regularly feeding on *Diadema*. We soon learned that numerous species rely heavily on *Diadema* for food. Randall (*1*) lists 22 species of fishes known to eat *Diadema*. Other predators are two species of helmet shells, *Cassis tuberosa* and *C. madagascariensis*, and the spiny lobster *Panulirus argus* (*2*). Schroeder (*3*) describes the attack behavior of *Cassis tuberosa*, and Cornman (*4*) describes the paralyzing saliva of this species.

Thus, *Diadema* is far from invulnerable, and like certain other aquatic animals subject to considerable predation (*5*) the species exhibits an alarm response, or Schreckreaktion, when stimulated with juices of injured members of its own species. Alarmed urchins mount on their ventral spines and race away for a meter or two, gradually slowing down and becoming quiescent again (Fig. 1, A–D).

One questions whether an escape response of an organism to intraspecific juices is necessarily related to predation. Perhaps the urchins might respond similarly to any chemical disturbance. *Diadema* stimulated in the field with dilute (5 percent) acetic acid show essentially the same escape behavior, and there is no need to invoke predation for response to this substance. However, when we tested the response of *Diadema* to the juices of other echinoderms we found few signs of reactivity, and it is perhaps puzzling that *Diadema* might find its own juices "irritating" but not the juices of many other species.

Clumps of *Diadema* resting on a sand bottom at the mouth of Massey Creek of South Bimini were subjected to juices of other echinoderms (Table 1) Fig. 1E). Each stimulus animal was placed about 25 cm upcurrent from a *Diadema* clump and pulverized with a crowbar. Responses were noted in the *Diadema* in the next 5 minutes, then a medium-sized *Diadema* was crushed at the same spot to demonstrate that the respondent *Diadema* were at least sensitive to intraspecific juices. Control experiments in which the plain sand bottom was pulverized with the crowbar upcurrent from *Diadema* did not produce locomotory responses.

In this survey only *Lytechinus variegatus*, another sea urchin, was clearly potent in producing a response in *Diadema*. However, in one experiment with juices of *Echinometra lucunter*, two respondent *Diadema* moved rapidly away. As the *Echinometra* crushed in this experiment were quite small, it seemed possible that lack of overwhelming response might reflect insufficient concentration of stimulus juices.

In other trials with weighed stimulus urchins (Table 2), *Diadema* was most reactive to intraspecific juices, fairly reactive to *Echinometra lucunter* juices, less reactive to *Lytechinus variegatus* juices, and quite unreactive to *Eucidaris tribuloides* juices. Even massive doses of *Tripneustes ventricosus* juices produced no clear response.

Although the response of *Diadema* to echinoderm juices may be an avoidance response to irritating chemicals, it is not obvious why intraspecific juices should be so especially irritating unless some factor other than pure "chemical stress" is involved. *Diadema* juices are apparently not irritating to the myriad fishes, crabs, and lobsters of the Bimini flats (Fig. 1, A–D). We suggest that the most reasonable explanation for the observed species specificity of response is predation.

Figure 1, A–D suggests how alarm behavior might help *Diadema* avoid predators. For this sequence a single urchin in a clump of 35 urchins was crushed. Alarm reactions immediately commenced in urchins downcurrent from the crushed urchin, but not in urchins lateral to it. After a couple of minutes the responding urchins had moved varying distances downcurrent, leaving a gap in the center of the original clump. If predators of *Diadema* tend to move only short distances between meals, urchins that move downcurrent in alarm may reduce their chances of falling victim to a predator at the expense of increased danger to other urchins closer to the predator but crosscurrent or upcurrent from him and unaware of his presence. For predators feeding in schools it would not be necessary to postulate that successive victims of a single predator be close together; several predators feeding adjacent to one another could produce an equivalent advantage in response. We emphasize that response is not limited to urchins immediately downcurrent from a crushed urchin, and can be seen