serum included by the clot and that less than 5 percent of plasma plasminogen is adsorbed by the clot. The results suggest that for therapeutic fibrinolysis the concentration of the agent intended to dissolve fibrin should be present in adequate concentration in plasma (*8*).

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Pain Threshold and Discrimination of Pain Intensity during Brief Exposure to Intense Noise

Abstract. Neither pain threshold nor the capacity to discriminate intensity of mild pain was significantly altered during simultaneous stimulation by intense "white" noise. These observations indicate that the reported clinical usefulness of such auditory stimulation during painful therapeutic procedures does not result from an alteration in the capacity to perceive pain.

Gardner *et al.* (*1, 2*) reported that appropriate use of apparatus which simultaneously presents stereophonic music and "white" noise is strikingly effective in reducing discomfort and need for local anesthesia during a variety of therapeutic procedures on the teeth, including extractions. The importance of relaxation, conditioning, and suggestion in modifying painful sensations and reactions is well recognized (*3*), and it has been reported that simultaneous presentation of an intense (140 db) 1000-cy/sec tone raised the pain threshold slightly, apparently by impairing the discrimination capacity of the observer through diversion of his attention (*4*). However, Gardner *et al.* concluded that stimulation with white noise was more effective in reducing pain than would be predicted solely as a consequence of these factors, and that "the noise directly suppresses pain" (*1*). They postulated that the massive barrage of impulses evoked in the auditory pathways by white noise may inhibit central neural aggregates concerned with pain, perhaps through interaction at the level of the reticular formation and thalamus (*2*).

To begin analysis of the mechanisms of this altered response to noxious stimulation, peripheral pain thresholds and discrimination of the intensity of mildly painful stimuli with and without simultaneous brief stimulation with intense white noise were contrasted.

Radiant energy was applied for 3 seconds to skin blackened with India ink at an intensity of from 120 to 240 millicalories per second per square centimeter. During a preliminary instruction period a painful stimulus was defined for the subjects, by demonstration, as one in which pricking pain was barely perceptible in the final instant of a 3-second stimulation. Room temperature was maintained between 22° and 25°C. Eighty stimuli, each to a different area of blackened skin on the volar surface of the forearm, were then successively applied by one investigator. The intensity of each stimulus was determined by another investigator who selected at random from a group of cards representing values from 120 to 240 millicalories. Neither the investigator applying the stimuli nor the subject was informed of the intensity of the stimuli. The range of intensities was selected to contain approximately as many stimuli above as below the pain threshold predicted from previous experiments. There were five cards for 120 mcal, five for 135, five for 150, and so forth. The subject's response to each stimulus was recorded as positive or negative for perceiving pain.

Every other thermal stimulation was accompanied with simultaneous stimulation by noise produced by a Grason Stadler 901-A generator with attenuation above 10,000 cy/sec at an intensity of 120 db relative to 2×10^{-4} dyne/cm^2 presented bilaterally through Permoflux PDR-8 earphones. The responses of a group of ten healthy medical students were ascertained. The group pain threshold was defined as the intensity at which pain was reported from 50 percent of stimuli. The threshold for this group (180 mcal/sec per square centimeter) agrees well with the thresholds reported previously from this laboratory (*5*). No significant

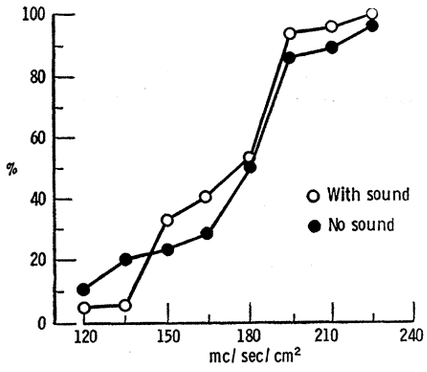

Fig. 1. Percentage of responses indicating that pain was perceived at various intensities of thermal stimulation. For each intensity five responses by each of ten subjects were ascertained. The group pain threshold is the intensity at which pain was reported from 50 percent of stimuli.

alteration in pain threshold as ascertained in this way was induced by simultaneous exposure to intense noise (Fig. 1).

To ascertain the effect of noise on discrimination of the intensity of mildly painful stimuli, pairs of blackened spots were placed on the forehead, the forearm, and the dorsal surface of the hand. The subject was asked to report whether a stimulus presented simultaneously with noise was more or less painful than a standard comparison stimulus presented without noise.

One spot in each pair was exposed to a standard stimulus of 235 mcal/sec per square centimeter without sound. The adjacent spot was then stimulated at an intensity selected at random from a fixed population ranging from 220

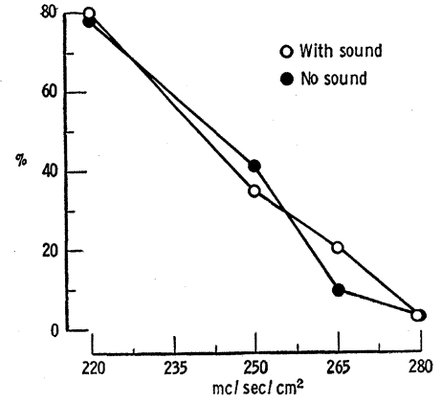

Fig. 2. Percentage of stimuli judged to be less painful than a comparison stimulus of 235 mcal/sec per square centimeter. Stimulation at this intensity was reported to be mildly painful by all subjects. For each intensity five responses by each of ten subjects were ascertained.

to 280 mcal/sec per square centimeter in increments of 15 mcal/sec per square centimeter, omitting the value 235. The subject was instructed to report "more" if the second (with sound) stimulus was more painful than the first (no sound) and "less" if the second stimulus was less painful. Each site on the skin was stimulated only once.

The responses of the ten medical student subjects are presented in Fig. 2. No differences in discriminations at any intensity or in any site approached statistical significance at even the 5-percent level of confidence.

It is concluded that under laboratory conditions brief simultaneous stimulation with intense white noise does not alter peripheral pain thresholds or perception of the intensity of pain resulting from mild, brief noxious stimulation.

These results are not necessarily contrary to the observations of Gardner *et al.*, since it is clear that neither pain threshold nor discrimination of the intensity of pain from brief, mild, stimulation is sufficient to describe all of the relevant aspects of the pain experience; for example, these aspects are not altered in patients in whom relief from the anguish of intractable pain has been achieved by surgical lesions placed in the frontal lobes of the cerebral hemispheres (*3*, *6*).

It is relevant to the interpretation of these results that they were made in a laboratory setting with intelligent, highly motivated subjects capable of sustained attention, and that the pain was always minimal and had little or no threatening significance. Thus they concern only the simplest sensory aspects of pain. The apparent discrepancy between these observations and the report of Gardner emphasizes the need to distinguish between pain as a simple sensation and those aspects that have to do with anguish, suffering, and threat. Concepts, terminology, and quantitative assay procedures are presently inadequate for investigation in the laboratory of this latter, most important, aspect of the experience of pain (*7*).

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Imidazole Aminoaciduria in Cerebromacular Degeneration

Abstract. Three families in which there are five patients with cerebromacular degeneration have been studied, and preliminary findings show that both the patients and some of the members of their immediate families have generalized imidazole aminoaciduria. The patients excrete large amounts of carnosine and anserine as well as histidine and 1-methyl histidine. The urinary defect appears to be transmitted as a dominant trait and the cerebromacular degeneration as a recessive trait. The fact that the two traits have been found in three unrelated families makes it likely that the two are manifestations of the same gene.

Carnosine and anserine, two peptides found in muscle, are present in urine in minimal amounts, 2 to 3 and 5 to 7 mg/day, respectively (*1*). We have found these peptides to be excreted at the rate of 20 to 100 mg/day in the urine of patients with a characteristic syndrome of cerebral degeneration and blindness variously described as late cerebromacular degeneration, juvenile Tay-Sachs disease, and Vogt's or Sjögren's disease. The patients also have an increased excretion of histidine and 1-methyl histidine, and a smaller but still abnormal excretion of a number of other unidentified ninhydrin reacting bases, of which several gave a positive Pauly reaction. The parents and siblings of the affected individuals have similar urinary abnormalities without the neurologic and retinal disease.

Carnosine is eluted almost concurrently with tryptophan and creatinine at 400 ml from the 50-cm column of the automatic amino-acid chromatography apparatus of Moore *et al.* (*2*), and anserine is eluted concurrently with 3-methyl histidine at 325 ml. Hydrolysis of the patients' urine made 4*N* in hydrochloric acid for 6 hours at 100°C, resulted in the complete disappearance of the carnosine and anserine peaks. The histidine and 1-methyl histidine peaks increased, and a new peak appeared at 580 ml on the 150-cm column and at 90 ml on the 50-cm column, corresponding to beta alanine. No new peak appeared in the region of gamma aminobutyric acid, showing that this urine does not contain large amounts of homocarnosine, first identified from brain tissue by Pisano *et al.* (*3*).

Figure 1 shows the pertinent area of the 50-cm column chromatogram of the urine of M.T., who had one of the two cases of cerebromacular degeneration which were found in one family. The urine sample used contained 10 μmole of alpha amino nitrogen as determined by the naphthoquinone method (*4*). Table 1 gives the values obtained for histidine, anserine, carnosine, and beta alanine before and after hydrolysis of this urine.

For 3 days M.T. was kept on a diet containing less than 15 mg/day of histidine with no significant change in the urinary excretion of the imidazole compounds.

Chromatograms of the blood of both M.T. and his brother D.T., who also has cerebromacular degeneration, show no unusual peaks. This suggests a renal abnormality in clearance of imidazoles rather than a specific enzyme block. The peculiar pattern of imidazole amino acid excretion also militates against a block in the histidine metabolic pathway.

As far as we know there have been no reports of an amino acid abnormality associated with cerebromacular degeneration, nor have there been any reports of excessive carnosine or anserine excretion in any disease entity. This is not the same syndrome as the histi-

Table 1. Conversion of carnosine and anserine to beta alanine and histidine by acid hydrolysis of urine. Values given are micromoles in 1.23 ml of urine.

Before hydrolysis	After hydrolysis	Difference	
		Actual	Theoretical
	Histidine		
1.18	5.05	+3.97	+2.89
	Anserine		
0.41	0.0	−0.41	
	Carnosine		
2.89	0.0	−2.89	
	Beta alanine		
0.07	3.71	+3.64	+3.30