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

dinuria described in Ghadimi *et al.* (*5*), for we have been able to examine a urine specimen (*6*) from a patient with histidinuria and find it to contain only histidine in excess, with no abnormal peaks in the areas of anserine, carnosine, or 1-methyl histidine. The cases of histidinuria show abnormal excretion of imidazole acids. Preliminary paper chromatographic studies of the urine of our two patients (M.T. and D.T.) also reveal an abnormal pattern. 1-Methyl histidine is excreted excessively in the nutritional muscular dystrophy which develops in rabbits on a vitamin-E deficient diet (*7*, *8*) and in human muscular dystrophy (*8*). There is no evidence of dystrophy in the patients or in their parents or siblings, who usually excrete more methyl histidine than the patients.

The excretion of 1-methyl histidine has been reported to parallel the intake of protein in normal individuals, unlike the excretion of other amino acids (*9*). We have some data also suggesting this. An unusually large protein intake might, therefore, tend to produce the results which we have seen in the families of these patients. Review of the dietary history in the T. family reported below, shows, on the contrary, a relatively small protein intake. Quantitative studies on the tolerance to imidazole amino acid intake are in progress.

Our findings are of considerable interest from a genetic standpoint. Figure 2 shows the pedigree of M.T.'s family. In this kinship there is no consanguinity. Only the two siblings, M.T. age 12 and D.T. age 8, show any neurologic or mental changes. M.T. at age 7 developed convulsive disease, decreasing mental function, and retinitis pigmentosa which has progressed almost to complete blindness. D.T., who first showed symptoms at 7 years, has mild retinitis pigmentosa with considerable loss of vision and has shown slight mental deterioration over the last 6 months. Two of the other three siblings have excessive imidazole amino acids in their urine, but have no neurologic or ocular disease. However, they have not yet reached the age at which the neurologic syndrome was first observed in the affected children. Both the father and mother of these children show similar urinary abnormalities, and a paternal uncle and his child also exhibit them, all with no evidence of the neurologic syndrome.

A similar genetic pattern has been found in two other families, in which three patients and three parents have been tested so far.

The strange finding of urinary abnormalities with no associated mental or neurologic changes in six out of eight of the immediate kinship tested suggests two possibilities. The first is that the cerebromacular degeneration may be unrelated to the imidazole abnormality. Of interest in this respect is the fact that the most marked excretion of 1-methyl histidine is found in the father and uncle, and the patient with the lesser degree of degeneration has the greater excretion of carnosine. These genetic traits are sufficiently rare that a concurrent finding of the two in one individual is highly unlikely. The possibility exists, however, that the imidazoluria is a dominant trait independent of the neurologic disease. The fact that three unrelated families show the same pattern makes this unlikely.

The second possibility, which seems to be the better explanation of all the observed facts, is that the imidazoluria and the neurologic disease are manifestations of the same genetic defect. The imidazoluria may be a dominant manifestation, and the neurologic disease a recessive trait. An imperfect analogy may be drawn to sickle cell trait and sickle cell disease. If we consider the clinical signs of sickle cell disease to be the recessive trait and the sickling of red cells to be the dominant expression, there is some similarity to the phenomena described in this report. A major difference exists, however, in the finding that the observed chemical abnormalities in the urine do not parallel the severity of the cerebromacular degeneration.

This syndrome resembles Hartnup disease (*10*) to some extent in respect to the aminoaciduria, for the plasma levels of amino acids in the cases tested are also normal, suggesting an abnormality of clearance of amino acids.

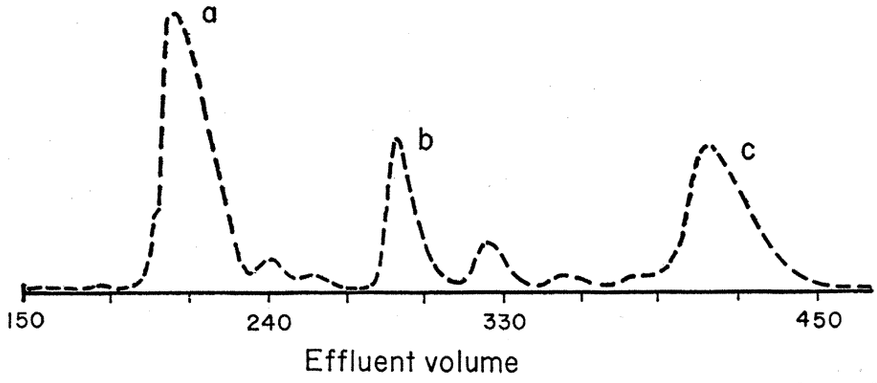

Fig. 1. Tracing of 50-cm column chromatogram starting at 150-ml effluent volume of *p*H 4.25 citrate buffer (*2*). Each division represents 30 ml. Peaks: *a*, ammonia, 5.35 μmole; *b*, histidine, 1.18 μmole; and *c*, carnosine, 2.89 μmole.

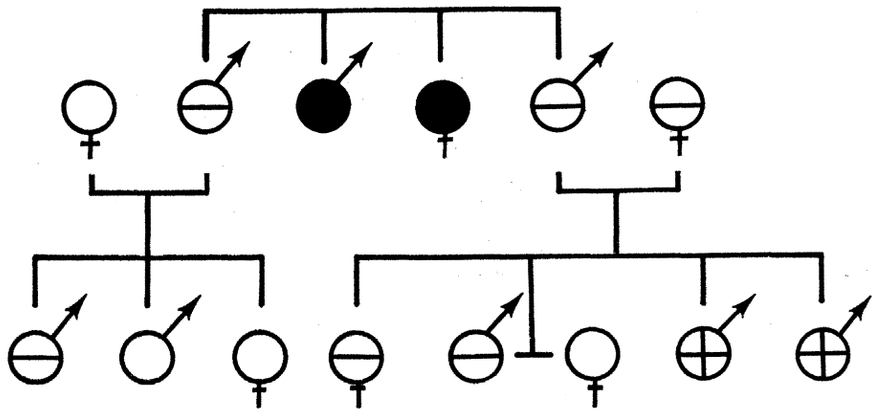

Fig. 2. Pedigree showing the distribution of imidazole aminoaciduria in males and females of two generations. Symbols: horizontal line, imidazole aminoaciduria; cross, imidazole aminoaciduria and cerebromacular degeneration; solid black, these individuals are dead, and there is no history of cerebromacular degeneration in either one.

Hartnup disease involves mainly the indole group of compounds, and the present cases show primarily imidazole aminoaciduria. The lesion in both diseases is probably one of transport. Studies of the problem are under way. A major difference between the two diseases is the apparent genetic dominance of the aminoaciduria in the imidazole syndrome (*11*).

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Electrostatic Fields: Their Effect on the Surface Tension of Aqueous Salt Solutions

Abstract. Electrostatic fields of up to 7000 volt/cm have been applied across air/solution interfaces by means of parallel-plate electrodes, and the resulting surface tension changes were obtained by measuring, through a balance linkage, the deflection of mica plates floating on the surface. Surface tension changes (always negative) of up to 0.5 dyne/cm have been observed in both distilled water and dilute sodium chloride solutions.

The potential drop which exists naturally at an air/solution interface has received but little attention, particularly when compared to that given the potential distribution at the metal/solution interface. Attempts to measure this potential drop have been made by Frumkin (*1*) and Kamienski (*2*), with conflicting results. Theoretical treatment, including surface concentrations and surface tension changes for solutions of ionic species, has been given by Onsager and Samaras (*3*) and by Falkenhagen and Schmutzer (*4*).

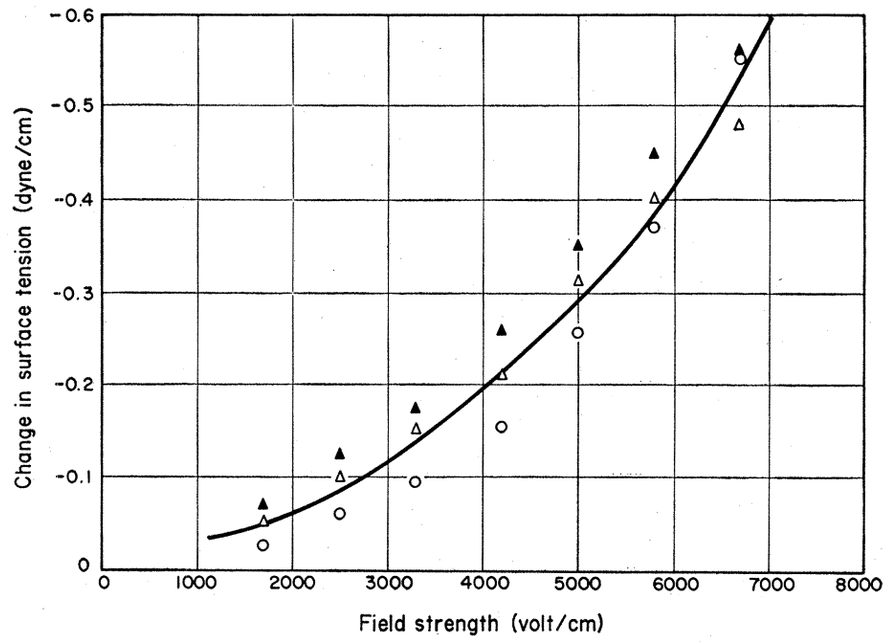

Fig. 1. Changes in surface tension of 3.5-percent NaCl solutions induced by electrostatic fields. Air electrode negative, mica float 7.3 by 12.8 cm, 4.5 cm in between plates; weight of float: solid triangles, 3.903 g; open triangles, 2.296 g; open circles, 1.942 g.

To our knowledge, the influence of impressed electrostatic fields on the potential drop and other properties of the air/solution interface has not been studied at all. As part of a research program supported by the Office of Saline Water, changes in surface tension induced by impressed electrostatic fields of up to 7000 volt/cm have been measured using distilled water and dilute sodium chloride solutions.

The measurements were carried out with a surface energy balance similar in design to one reported by Allan and Alexander (*5*), but modified slightly to permit application of the field across the interface. The movement of a sheet of mica floating on the surface with only one edge inside the field was used to detect changes in surface tension. Calibration by means of force/area curves with films of fatty acids showed a sensitivity of about 5×10^{-3} dyne/cm. Precautions such as complete isolation of the entire apparatus from the laboratory atmosphere and repeated skimming of the surface to remove traces of surface active materials were necessary to obtain reproducible and dependable data.

Application of the electrostatic fields gave rise to forces on the mica float other than the surface tension change. These forces, one a gravitational force due to lifting of the water by the field, and the other an attractive force on the float itself, were corrected for by using floats of various lengths and widths, changing such factors as mass, length of working edge, and area inside the field. It was found that after the proper corrections were made to the measured deflections, a consistent and reproducible force remains, which must be due to a change in surface tension induced by the applied field. The results for a negative air electrode, with 3.5-percent NaCl solutions, are shown in Fig. 1; the three types of points represent runs made with different floats. Similar data have been obtained for other solutions and for the air electrode positive. While there is considerable variation in magnitudes of the surface potential changes, all curves show the same general trend, that is, negative surface tension changes and a slight upward curvature with increasing field strength.

The results of these experiments are interpreted in terms of orientation of water dipoles under the influence of the applied field. If one accepts the value of field strength of 10^7 volt/cm which has been proposed by Kamienski (*2*) as already present in the water/air interface, then it is difficult to understand how application of an external field of less than 10^4 volt/cm can have