on human and experimental amyloidosis, 1959, M.S. Thesis, Univ. of Illinois, Chicago.

6. Lathvalati, J., *Acta Endocrinol.* (Kbh)., suppl., 1953, 16.

7. Pirani, C. L., Bestetti, A., Mombelloni, P., Catchpole, H. R., *Atti X Congresso Lega Internat. Contro il Reumatismo,* 1961, v2, 912.

8. Loevy, H., *Anat. Rec.,* 1963, v145, 117.

9. Fraser, F. C., *First Internat. Conf. of Cong. Malformations,* 1960, p179.

10. Kalter, H., *Genetics,* 1954, v39, 185.

11. Weichselbaum, T. E., *Am. J. Clin. Path.,* 1946, v16, 40.

12. Jencks, W. P., Jetton, M. R., Durrum, E. L., *Biochem. J.,* 1955, v60, 205.

13. Block, R. J., Durrum, E. L., Zweig, G., *A manual of paper electrophoresis,* Acad. Press, New York, 1955.

14. Walker, B. E., *2nd Annual Meeting of Teratology Soc.,* 1962, p11.

15. Clark, K. H., *Genetics,* 1956, v41, 637.

Received April 4, 1963. P.S.E.B.M., 1963, v113.

Iontophoresis of Potassium for Experimental Determination of Pain Endurance in Man.* (28427)

F. B. BENJAMIN and W. M. HELVEY

Space Environment and Life Sciences Laboratory, Republic Aviation Corp., Farmingdale, L. I., N. Y.

The value of experimental work with pain sensation has been a subject of heated debates for many years. Beecher(1) pointed out that the difficulty is largely based on differences between clinical observations and conclusions drawn from laboratory experiments. According to definition pain is a disagreeable sensation. However, the threshold pain used almost exclusively in laboratory experiments can hardly be considered disagreeable. If in daily life we bump an elbow or touch a sharp instrument producing threshold pain, it would probably not even be considered as pain by the subject. Clinical pain has an inherent threat content, which is absent under experimental conditions. Beecher(1) shows that clinical pain varies considerably between subjects, while Hardy(2) in carefully controlled experiments showed that threshold pain is a constant factor. Therefore it is felt that experimental tests of pain endurance may be closer to clinical pain than tests of threshold pain.

Theoretically, a test of pain endurance should comply with the following criteria: 1. The test should be specific for pain sensation. 2. The stimulus should be well controlled and accurately measurable. 3. There should be a direct relation between measured intensity of the stimulus and resulting intensity of pain sensation. 4. The test should be reproducible and variations should represent physiological variability of pain sensation. 5. The test should produce a minimal degree of tissue damage and there should be no danger of severe or lasting injury. 6. The equipment should be simple, rugged and inexpensive.

In earlier work(3) various tests were used for pain endurance. However, none of them are suitable for evaluation of interpersonal differences. On immersion of the hand in ice water, fluctations of pain sensation are observed, rather than a steady increase with time. Therefore, time of immersion is no indication of pain intensity. Using heat as the stimulus, burn injury is produced at 50°C, while the endurance limits are reached only at 60°C. The same danger of injury prevents the use of electrical stimulation of the tooth. In ischemic contraction a blood pressure cuff, inflated to 200 mm Hg, is applied to the upper arm and the rhythmic hand contractions against a fixed resistance are counted. This method works well for evaluation of drug effects where each subject serves as his own control. However, it is not suitable for determination of interpersonal differences, as the threshold varies with muscular development so that the mean endurance limit for females is lower than the threshold for males.

On the basis of previous experience with iontophoresis of potassium(4), this method

* Partially supported by NASA grant.

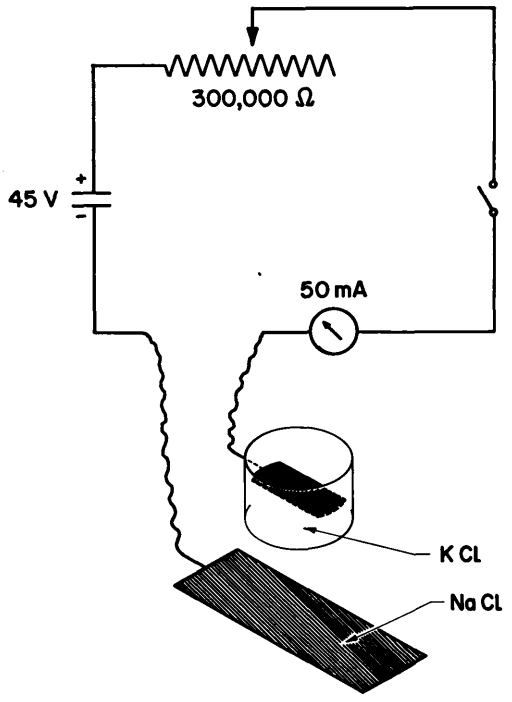

FIG. 1. Diagrammatic presentation of method.

appeared to be suitable for experimental production of endurance pain. Iontophoresis uses the repulsion of the positive potassium (K) ions by the positive pole of a direct electric current to drive the ions into the skin. The number of ions depends upon the current and time, and is independent of the concentration and of skin resistance. The potassium cannot do any harm as the total amount transferred at the highest pain endurance encountered is 0.025 g equivalents. The actual arrangement is shown in Fig. 1 and 2. A ring is fixed to the flexor surface of the forearm by means of elastic bands. In the ring is a metal plate, which is the anode of a D.C. electric current. The container formed by ring and underlying skin (14 cm^2) is filled with potassium chloride which is the contact medium between electrode and skin. The cathode is a large (6:12 cm) silver-silver-chloride plate with a rubber base and covered with several layers of saline saturated gauze. It is fixed to the flexor side of the arm using the same rubberbands as for the anode (Fig. 2).

In our experiments the current was increased by means of a rheostat at the rate of 5 mA every 15 seconds. When reaching the tolerance limits the current was turned down at once, but slowly. This causes immediate pain relief. Any sudden interruption causes a local shock which is not harmful but disagreeable. If the current is started at low intensity and then steadily increased, there is no sensation in the beginning. Soon there is a burning pain which increases slowly. At very high intensities a feeling like a muscle cramp may appear which may go far beyond the area of application. Endurance limits vary considerably from subject to subject but are repeatable for the same subject. Unbearable pain is mostly reported long before the cramp condition is reached. A galvanic current of the intensity and rate of change used in these experiments does not produce pain sensation.

TABLE I. Variability of Test in Same Subjects. (5 subjects, 10 tests within 13 days.)

Subjects	Mean (in V)	S.E.
I	23.05	.36
II	19.79	.54
III	11.22	.58
IV	20.72	.85
V	19.76	.72

Table I shows the intra- and inter-subject variability of 10 determinations in 5 subjects over a 13 day period. Intra-subject variability is small and differences between subjects are marked. This is considered an indication that physiological and psychological differences of pain endurance may be demonstrated by this technique.

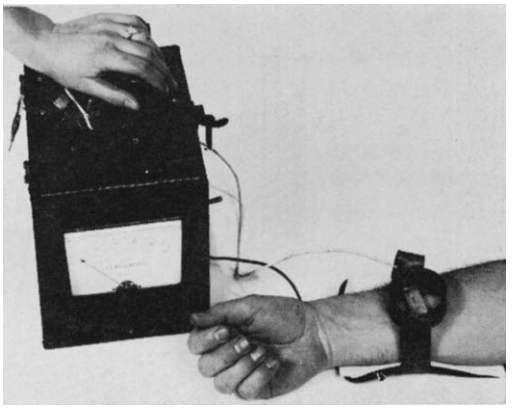

FIG. 2. Application of electrodes to subject's arm.

Recently a study was completed in our laboratory on the possible relationship between the intensity of a person's sensory experience and his ability to withstand a condition of prolonged exposure to sensory deprivation, isolation, and confinement. This investigation involved a study of pain endurance by the iontophoresis method. The pain tests were applied several days before and again immediately before the sensory deprivation experiments. It was found that the 13 subjects who did not give up during 34 hours of sensory deprivation had a pain endurance rating of 27.0 $\pm$ 3.28 mA, while the 10 subjects who asked prematurely for release had a rating of 14.0 $\pm$ 1.64. This difference is significant ($p>0.05$).

Discussion. In previous work(4) evidence was presented that an injurious stimulus (thermal, mechanical, chemical, or electrical) is associated with release of intracellular potassium (K). As according to Brown and Feldberg(5) and others, K is a marked nerve stimulus, it is assumed that the K ions released on injury are the cause of pain sensation. Experimental evidence indicates that agents or processes which facilitate K release (for instance, histamine) are painful, and agents or processes that inhibit K release (for instance, cortisone) decrease pain sensation. If calcium is used instead of potassium there is no pain but marked vasodivatation. The difference between K and Ca ions cannot be due to the difference of valency. As current flow depends on ion transfer, bivalent Ca ions have the same concentration and the same rate of transfer as monovalent K ions.

It cannot be assumed that K has any special affinity for pain fibers. The specfic pain response in these experiments may be due to the superficial position of pain receptors compared with the deeper receptors for temperature sensation.

In our experiments chloride salts were used. As the area for the cathode is large (5 $\times$ anode) the density of ions per unit area is low and there is no sensation in this area. If the exposure area is cut down to the same size as the anode a pricking sensation occurs which increases with the intensity of the current.

The data are considered evidence that group differences of pain endurance can be measured and expressed in a quantitative way with this test. At this time it is not known whether the observed differences are due to differences of pain sensitivity or due to differences of motivation and will power. However, the same difficulty exists in clinical pain, where according to Beecher(1) the pain intensity of a subject is largely determined by his attitude towards the pain producing process.

Summary. Release of intracellular potassium is considered the physiological stimulus of pain production in tissue injury. Iontophoresis simulates this physiological mechanism. Therefore, it is specifically a painful stimulus. It is well controlled. The intensity of the stimulus corresponds to the intensity of pain sensation. It gives reproducible values and it causes a minimal degree of tissue damage. Therefore, iontophoresis is well suited for pain endurance measurements. However, it will not simulate the threatening content of clinical pain. Experimental data indicate that day to day variability in the same subject is small, while differences between subjects and between groups may be large.

1. Beecher, H. K., *Pharm. Rev.,* 1957, v9, 59.

2. Hardy, J. D., Goodell, H., Wolff, H. G., *Pain Sensation and Reactions,* Williams & Wilkins, Baltimore, 1952.

3. Benjamin, F. B., *Science,* 1958, v128, 303.

4. ———, *J. Appl. Physiol.,* 1959, v14, 643.

5. Brown, G. L., Feldberg, W., *J. Physiol.,* 1935, v84, 12P.

Received April 8, 1963. P.S.E.B.M., 1963, v113.