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A device for measuring the threshold of pain in man

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1. A device operated by hand has been constructed for the controlled compression of the soft tissue in front of the Achilles tendon.

2. The sensitivity of the device was sufficient to demonstrate the analgesic action of 0.3 g aspirin.

There are several methods of producing experimental pain in man. Hardy, Wolff & Goodell (1940) used a 1,000 W lamp focused on the blackened forehead for 3 sec. This produces a pain like a superficial burn. Armstrong, Dry, Keele & Markham (1951) formed a blister on the skin by the application of cantharidin. The method requires the production of only a small blister, but there are aesthetic objections. Deneau, Wand & Gowdey (1953) applied a sphygmomanometer to the middle of the calf and inflated it till it caused pain. They were able to show analgesia due to aspirin, codeine and pethidine. This method causes deep pain similar to that encountered in clinical practice. An electrical method involving stimulation of the earlobe was devised by Siker, Swerdlow & Foldes (1954), but it has not been much used. Benjamin (1958) put a sphygmomanometer cuff round the subject's arm and raised the pressure to occlude the blood flow. The length of time for which the subject could tap with his index finger was then measured. Williams (1959) showed the effectiveness of this method and studied the variation in response of eighteen subjects to aspirin and similar drugs.

Hewer, Keele, Keele & Nathan (1949) attempted to measure analgesics using natural pain—that is, in patients suffering from severe pain of some sort. It is evident from their paper that a patient has a great deal of difficulty in remembering the intensity of a pain some hours before, or in trying to judge a degree of alleviation in a pain. It is much easier to appreciate that a pain has been completely relieved or that it has not.

The present apparatus was devised as a cheap instrument suitable for use by students, which reproduced a type of pain that could be elicited manually and which the students would know about.

Methods

Apparatus

A device for the controlled compression of the soft tissue in front of the Achilles tendon is shown in Fig. 1 and a diagram is shown in Fig. 2. The device is made

in two parts joined together at the pivot V. When the handles are brought together the knobs P and Q are separated. The knobs may then be placed around the tissue to be compressed. When the handles are separated the knobs come together, but their motion is limited by the construction of the joint which contains a projection W to act as a stop. Thus when the handles are separated against the stop the knobs P and Q press on the tissue to a limited degree.

The knob P is mounted on a screw S (1 mm pitch) which can be turned by the knob R. The screw is threaded through the housing M, so that P may be advanced or retracted.

The knob Q is mounted on a plunger which is spring-loaded. The spring exerts a tension of 10 kg when compressed by 13 mm. The spring is concealed in the housing N. At the other end of the plunger (from the knob Q) is a projection T which bears against the plunger (U) of the dial gauge. In this way the degree of compression of the spring is recorded by the dial gauge (Batty CC1–13 mm by 0.1 mm).

The knob Q is shown in Fig. 1 pressing on the tissue behind the lateral malleolus. The handles have been separated as far as possible and the movement is limited by the stop. It may be noticed that the knob is making some indentation into the skin and the dial gauge is reading 4 units. The pain threshold in this subject was 60 units.

Method of use

The subject is seated. He removes his shoe and sock and rests his leg on a stool so that his ankle projects over the edge. The two knobs P and Q are applied to

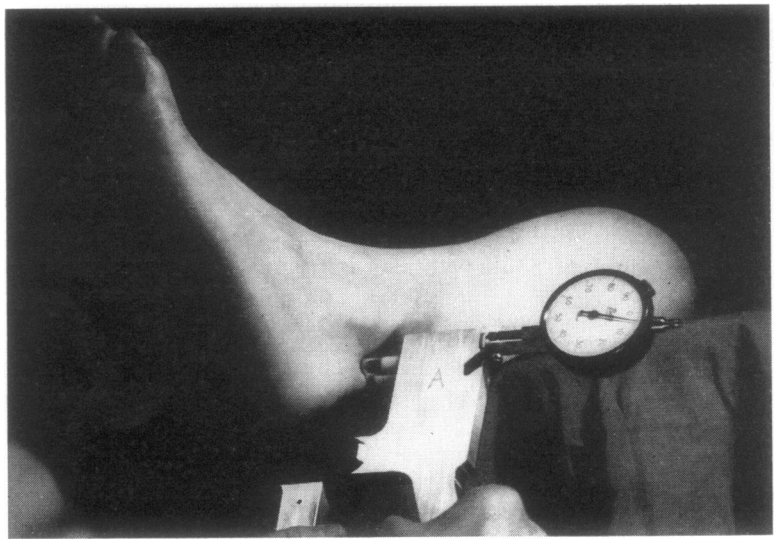

FIG. 1. Application of the device to the ankle. The Perspex knob can be seen depressing the skin behind the lateral malleolus and in front of the Achilles tendon. The dial gauge reads 4 units. The handles are fully separated against the stop.

the soft tissue in front of the Achilles tendon a little way above its insertion into the calcaneum (see Fig. 1). The site to be used should be marked on the skin on each side, as the sensitivity varies with position.

A preliminary adjustment of screw S is made so that when the handles are fully separated the knobs P and Q depress the skin to a small extent without causing pain. Screw S is then advanced gradually, obtaining a reading on the dial at each advance. This reading is recorded together with a note on the response of the subject. The device is applied at intervals of 10 sec. The subject will indicate when the application of the device causes pain. Further trials can then be made to bracket the threshold.

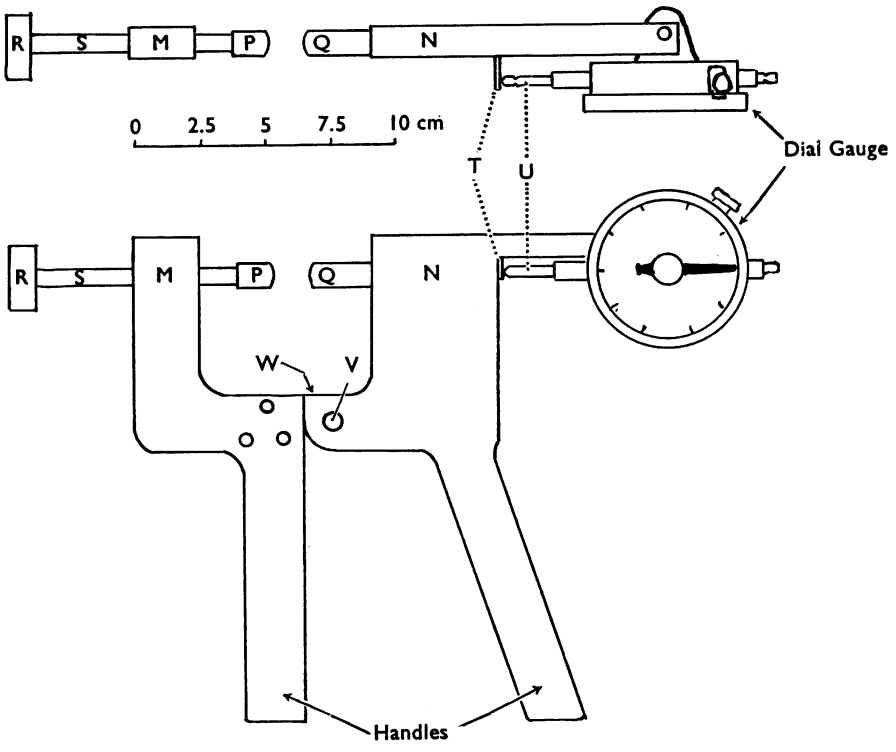

FIG. 2. Side view and top view of device, drawn to scale.

TABLE 1. *Method of determining the threshold from a series of dial readings*

Reading No.	0 min	20 min	40 min
1	11–	40–	44–
2	20–	59–	51–
3	31–	68+	64+
4	40±	70+	53+
5	48–	52–	42–
6	60–		
7	63±		
8	69+		
9	63+		
10	49–		
Means	64, 56	63, 61	57, 47
Threshold	60	62	52

Method of determination of threshold

An example of the method of determining the threshold is given in Table 1. This shows three determinations at intervals of 20 min. At the first determination, the first dial reading was 11. This did not cause pain—indeed the subject barely noticed it—so the dial reading was recorded, together with the negative sign. The device was then removed from the ankle, the screw S advanced by two turns, preferably out of the subject's sight, and reapplied, taking care to employ the marks on the skin. The second reading was 20 and again there was no response. At the fourth reading the subject evidently felt something, but he was doubtful that this was really pain, so the doubtful response (±) is used. The screw S was again advanced but the next reading gave no pain.

Eventually a level is reached at which the subject is in no doubt that the device is painful and this is indicated by the positive sign. At this point the screw S is retracted, by one turn at a time, and the device again applied, till the level of no response is reached.

The threshold is bracketed both as the screw S is advanced and again as it is retracted. The means are taken of the two sets of readings, any doubtful readings (±) being ignored. Thus in the first determination in Table 1 readings 6 and 8 give one mean, and readings 9 and 10 give the other, reading 7 being ignored. The mean of these two means then gives the threshold.

Results

Doses of soluble aspirin BP were dissolved (or suspended) in 50 ml. of water and were administered to healthy volunteers. Three experiments using different doses in subject A are shown in Fig. 3, which gives the time course of the percentage rise in threshold. The aspirin was administered at zero time just after the first determination of the threshold. It is difficult in Fig. 3 to display the normal variation in threshold, each curve being related to the particular initial reading, which statistically is not justified ; this introduces an additional cause of variation in the curves

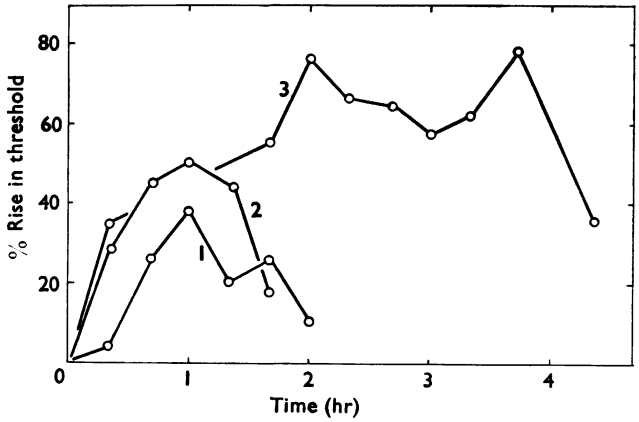

FIG. 3. Time course of increase in pain threshold after administration of aspirin. Curve 1, 0.3 g ; curve 2, 0.6 g ; curve 3, 1.2 g.

which cannot be controlled. The considerable rise in threshold that aspirin can produce is, however, demonstrated, as is also the length of time for which a measurable increase may be followed.

Subject B received a dose of 0.9 g aspirin on two separate occasions, the pain threshold being followed for 2.5–3 hr. Means were calculated at corresponding times after ingestion of each dose and standard deviations were determined for each mean. These are expressed in Fig. 4 by the series of vertical lines. These means have to be compared with the pain threshold which is found when no drug has been administered. Five such determinations obtained on 4 different days gave a value

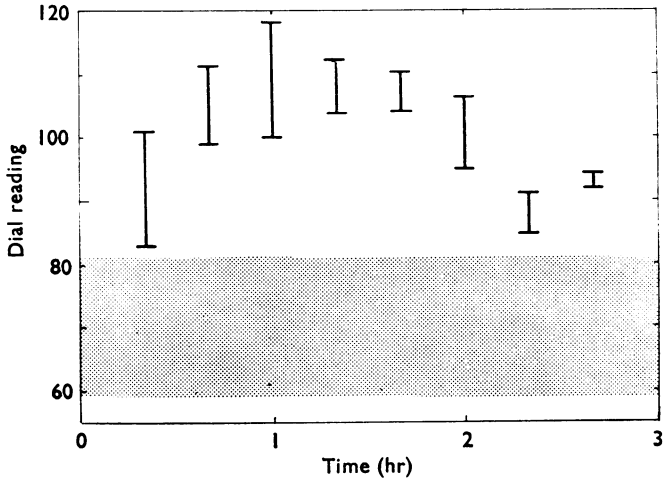

FIG. 4. Effect of a dose of 0.9 g aspirin on subject B. The shaded area between the horizontal lines encloses the measurements recorded when no drug was administered (mean ± S.D.). The vertical lines represent the means (± S.D.) of two separate experiments.

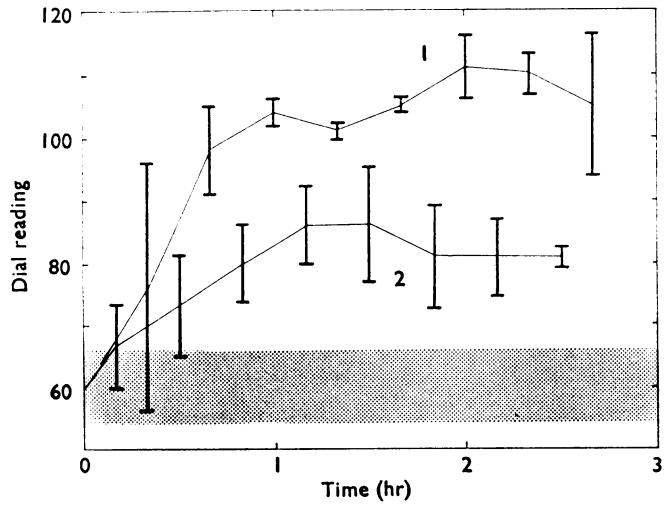

FIG. 5. Effect of a dose of 0.9 g aspirin and of a dose of 0.3 g aspirin on subject C. The shaded area encloses the results with no drug (mean ± S.D.). Curve 1, 0.9 g; curve 2, 0.3 g.

of 70 (S.D. 11), and this is shown in Fig. 4 as the shaded area. It is evident that there was a considerable rise in the pain threshold, the highest level being reached in 1 hr, after which the level fell slowly and reached the resting level in about 3 hr.

The significance of the rise in pain threshold in Fig. 4 may be calculated by comparing the mean threshold when no drug was given with the 5 pairs of threshold determinations at 40 min, 1 hr, 1 hr 20 min, 1 hr 40 min and 2 hr. The analysis gives $t=8.75$ and for $n=13$, $P<0.01$.

Subject C received a dose of 0.9 g aspirin on two occasions and a dose of 0.3 g on two further occasions. On a fifth occasion no drug was administered. The results on subject C are given in Fig. 5 and confirm the impression given by the experiments in Fig. 3, namely that a larger dose gives a larger response. The shaded area represents the mean (and S.D.) of the threshold when no drug was given. The heights of the vertical lines indicate the difference between the two experiments, and sometimes this difference is large. The experiments selected for the figures were those with small differences between the pair of experiments.

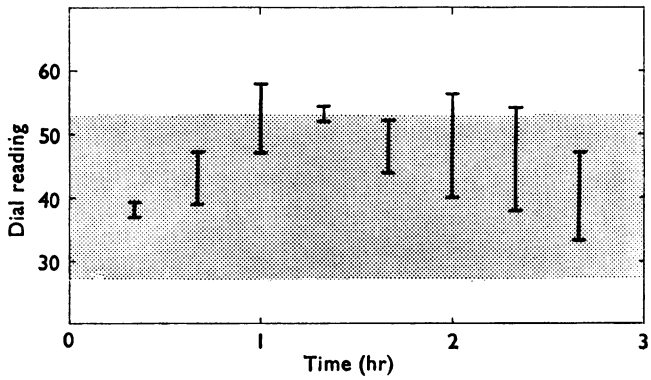

FIG. 6. Effect of a dose of 1 g paracetamol on subject D. The shaded area encloses the results with no drug (mean ± S.D.). The response is within the shaded area.

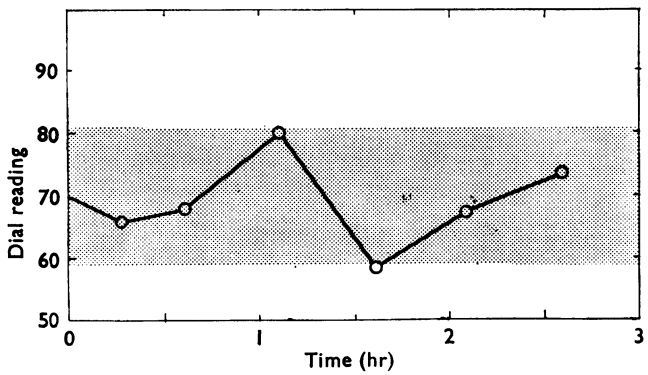

FIG. 7. Effect of a dose of 0.9 g aspirin on subject B, when the aspirin had not been dissolved in water before administration. The response is not significantly outside the shaded area (compare Fig. 4).

Studies on a number of subjects indicated that there was a limitation on the maximum response that could be safely elicited. This limitation may be called bruising, the pain produced by the application of the device not being relieved the instant the device was removed but being prolonged for 5 sec. Moreover the threshold fell progressively to below the original level. A sufficient precaution was to limit the number of painful applications of the device to thirty during 1 day.

Subject D received 1 g paracetamol BP dissolved (or suspended) in 50 ml. of water on two occasions, and these results have been combined and compared with four determinations of the threshold when no drug was given. The comparison in Fig. 6 indicates that the threshold in this subject did not rise far and that the individual means did not exceed even the 68% confidence limits. There is, however, a slight increase in pain threshold which reaches a maximum at 1 hr 20 min which suggests that some drug has been administered (absorbed ?). This result compares well with the subject's own observation that paracetamol did not work on her. Experiments on other subjects showed that this was an exceptional result and that a dose of 1 g paracetamol increased the pain threshold by a mean of 65%.

A very small rise in pain threshold was produced when the drug (either aspirin or paracetamol) was not previously dissolved (or suspended) in water but the dry tablets were swallowed directly. Such an experiment on subject B is shown in Fig. 7, which indicates no increase in threshold. Similar results were obtained in other subjects, some of which showed a slow increase in threshold, suggesting poor absorption of the tablets.

Discussion

Character of the pain

The pain that is felt when the threshold is exceeded is of a dull character, relatively slow in onset though relieved as soon as the compression is released. It can be compared with the feeling of a headache so as to indicate a deep pain. It develops within 1 sec of the beginning of the compression, but it is apparent to the subject that the onset is not quite instantaneous, not like, for example, the application of heat to the skin.

The subject cannot distinguish between the normal pain and the pain produced under analgesia, so provided the drug used is not in a large enough dose to cause side reactions he cannot appreciate the potency of the drug. An increase in compression in the vicinity of the threshold gives a much more than proportionate increase in pain, perhaps as much as twice the pain for an increase of 10% in the compression, so the subject will not conceal the pain he feels, after the first few applications of the device.

It is important not to ask the subject to detect too small a change in the degree of pain. He can differentiate pain from no pain but he cannot appreciate the pain increment corresponding to one division on the dial gauge—a minimum of five divisions is necessary. When the pain begins to be felt there is an intermediate stage lasting over ten divisions in which the subject can appreciate that the device is more than touching but without the sensation that he is accustomed to call painful. The doubtful response ($\pm$) is thought to correspond to this intermediate stage and this is perhaps the threshold. As a subjective phenomenon it is hard to define and it is easier to bracket the threshold by detecting pain and no pain.

Rate of onset of analgesia

The rate of onset of analgesia caused by a drug given by mouth depends on the rate of absorption in the stomach, the rate of formation of the active principle (if this is not the drug), the rate of excretion and of detoxication and the rate of penetration of the blood–brain barrier. Variations in the several rates give rise to the observed variations in personal response. The effect of not dissolving the tablets in water before administration is shown by comparing Fig. 7 with Fig. 4. Authors commonly do not make it clear whether they dissolved in water the tablets administered or gave them before or after meals, so experimental studies often do not demonstrate the analgesic action of aspirin. If it were necessary to use the curve in Fig. 7 as the sole evidence of analgesia it would have to be compared with a placebo or reference compound, because the analgesia is of such a small extent. The experiments described in this paper make it clear, however, that when the tablets are given in water on an empty stomach, aspirin produces considerable analgesia. Experiments have not been done in which tablets were given in water on a full stomach, but clinical practice suggests that the analgesia takes longer to appear.

Experimental pain is commonly studied by men. Many women, on the other hand, experience pain every month with their menstrual cycles and sometimes also when they ovulate, so they have frequent opportunities to try out different drugs and to explore different methods of administration. If a particular drug is administered in an unsuitable way the woman does not obtain relief and consequently suffers many hours of pain. This reinforces the importance of proper administration of the drug, a form of feedback which is not obtained even with the present device. Beecher (1957) in an important review seemed to show that men were relatively unsuccessful in testing drugs with experimental pain. Possibly this is because they have less experience with personal pain.

Conclusion

The device described is cheap, robust and suitable for student use. Although applied in the vicinity of the Achilles tendon it does not cause pain on walking. Its precision is limited by the capacity of the subject to detect small changes in pain. A dose of 0.3 g aspirin, however, produced a rise in the pain threshold of 43%.

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