Quantitative Studies on Pain Threshold after Administration of Various Drugs

*By David I. Macht and Moses B. Macht**

INTRODUCTION

A suitable method for quantitative measurement of the analgesia (as distinguished from local anesthesia) produced by various physical and chemical agents is a crying need of modern experimental physiology, pharmacology and psychology. The old procedure in which psychologists tested pain sensation by the prick of pin or needle applied with varying pressure is obviously neither adequate nor scientifically accurate. The best method for measuring graded pain stimuli in human beings is undoubtedly the electric procedure in which a faradic or induction current is applied to the integument with fine electrodes and the minimum amount of energy required to produce a sensation of pain is determined. Such a method was devised and employed by Macht, Herman and Levy in 1916 in connection with their studies on the comparative analgesia produced by the opium alkaloids and their combinations (1, 2). This method is still regarded as that most satisfactory for quantitative comparison of the effects of

* Pharmacological Research Laboratory, Hynson, Westcott & Dunning, Inc., Baltimore, Md. and the Department of Psychology, Johns Hopkins University

well-known, non-toxic drugs on human beings. In this test Macht, Herman and Levy employed a large inductorium calibrated both in the old Kronecker units (3) and also in terms of absolute C. G. S. units. For investigative work on the analgesia of new drugs and chemicals, the clinical toxicity of which has not yet been explored, however, the method mentioned above is unsuitable because of the obvious hazard involved in experimenting on human subjects. Search was therefore made for some other quantitative means of testing analgesia on lower animals. Employing the same method as that used for human beings, the senior author attempted to determine pain thresholds on guinea pigs. This method proved fairly satisfactory in connection with a study of cobra venom analgesia and is described in detail elsewhere (4). Briefly, the procedure was as follows: A small area of skin on the back of the animal is carefully shaved and the threshold of pain for some point in this area is determined with fine electrodes transmitting a graduated faradic current. When the intensity of the faradic current elicits pain, the animal squeals; and the pain threshold thus determined by experienced hands is

fairly constant. However, several difficulties arise in connection with such a guinea-pig method. In the first place, the animals are inconvenient to handle; in the second place, some of them squeal from fright even when suffering no pain. Furthermore, the pain threshold for the skin on the back of the guinea pig is too high; that is, it requires a powerful stimulation to elicit pain. More recently, the present writers have designed a more suitable method, in which rats are employed instead of guinea pigs, for quantitative study of pain thresholds in animals. It is this new method which is described in the present paper.

EXPERIMENTAL

THE RAT METHOD

In connection with experimental psychological studies on albino rats, it was discovered that the scrotum of adult male rats is very sensitive to faradic stimulation so that the application of fine platinum electrodes to any spot on its surface elicits sharp pain. In this way the threshold of pain for rats can be accurately determined and measured. While an assistant holds the animal gently but firmly, the investigator applies the electrodes at some convenient point on the surface of the scrotum. The faradic current is slowly increased and when the animal receives the first sensation of pain (i. e., when the pain threshold is reached), it utters a characteristic squeal. A normal rat never squeals when merely handled. The pain threshold for any point on the surface of the scrotum is quite constant for at least twelve hours and indeed will be found generally to be the same on the following day unless in the interim the rat has been treated with some pharmacological agent. Figure 1 shows the various areas found most convenient for such determination of pain thresholds. The electrodes may be applied either over the body of the testicles (A and B) or at their tips (a and b). Two other convenient spots even more sensitive for the electrodes are over the septum (indicated by the letters C and D).

Such a "faradic rat method" has been found particularly convenient for measurement of pain thresholds because the scrotum is rich in sensory nerve endings and is much more sensitive to pain stimuli than the skin of the guinea pig. Furthermore the anatomical structure of the scrotum enables the experimenter to distinguish between a general analgesic effect and a purely *local anesthetic* action of a drug. There are two sets of muscles in the scrotum. Some of the muscle fibers in its wall are an extension of the cremasteric muscle; in addition, the so-called dartos tissue itself is composed of muscle fibers. When a *strong* electric stimulus is applied
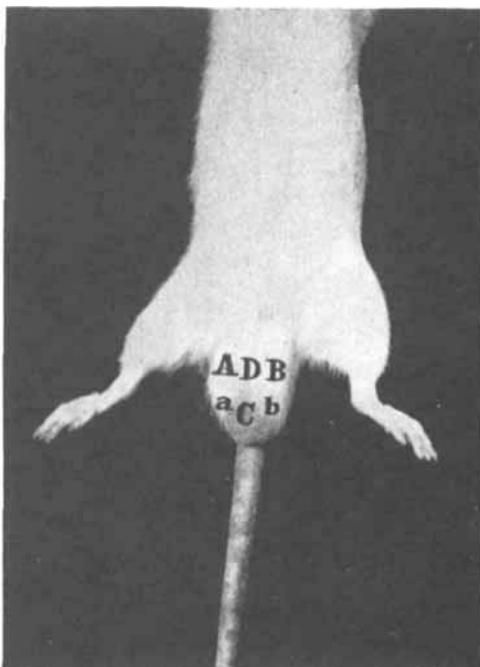

Fig. 1.—Illustration showing site of application of the electrodes in the rat method.

to the surface of the scrotum, pain is elicited not only by direct stimulation of the nerve endings but also by the powerful contractions of the cremasteric and dartos muscle fibers. If a drug is a powerful analgesic, neither the direct stimulation of the sensory nervous apparatus nor the contraction of these muscles and compression of the testes will suffice to elicit pain and cause the rat to squeal. On the other hand, if a local anesthetic is injected intradermally at any point on the scrotum, the failure of a weak electric stimulus to produce a response will indicate local anesthesia, but a stronger stimulus will cause such powerful contraction of the muscles as to elicit pain in the unanesthetized areas and wring a cry from the animal.

Apparatus and Physical Considerations.—In employing the new rat method for determining pain thresholds, the writers made use of the well-known and popular Harvard inductorium. This instrument is constructed of hard rubber and metal. The primary coil is wound with double silk-covered wire, 0.82 mm. in diameter, having a resistance of 0.5 ohm; and its core consists of ninety pieces of shellacked soft iron wire. The secondary coil, which can be moved on two parallel brass rods 22 cm. long, contains 5000 turns of silk-covered wire, 0.2 mm. in diameter. Each end of the secondary wire is fastened to a brass bar screwed to the end of a hard rubber spool. In operating the inductorium, the writers employed a dry cell of 1.6 volts. The intensity of the faradic current was varied, of course, by sliding the secondary toward or away from the primary coil and measuring its distance in centimeters. The effects of drugs on the pain threshold

can be roughly expressed by stating the relative position in centimeters of the secondary to the primary coil. Since this does not convey an adequate idea of the magnitude of the stimuli, when two such thresholds are compared, the authors, with the aid of a distinguished professor of physics, have calibrated their apparatus in absolute physical units and plotted a curve showing the relation between position of the secondary coil to actual voltages for each position. To indicate the vast increase in electromotive force obtained when the secondary is brought closer to the primary coil, it is instructive to dwell briefly on the physical principles of the induction coil.

The induction coil is a device for obtaining induced electromotive forces of high value from an ordinary battery circuit. It consists of a primary coil of, say, n^1 turns of thick copper wire so as to have a small resistance, wound about a central core composed of a bundle of soft iron wires. The coil is connected into the circuit of a battery through the contact point at the end of a set-screw. Outside the primary and thoroughly insulated from it is the secondary coil, consisting of n^2 turns of fine wire, the ends of which come to two insulated posts supporting the discharge electrodes. An iron armature or hammer is provided to make and break the circuit of the primary coil automatically.

If the hammer is held away from the opposite contact point, then touched to this point, and again pulled away quickly, a spark will be seen to pass between the discharge electrodes at the *break* only— *not* at the make. The reason for this is that, on account of the opposing influence at *make* of self-induction in the primary, the magnetic field about the primary rises very gradually to its full strength and hence its lines of force, figuratively speaking, pass into the secondary coil comparatively slowly. At *break*, however, by separating the contact points very quickly, the current in the primary can be made to fall to zero in an exceedingly short time, perhaps not more than 0.0001 second; that is, all its lines of force can be made to pass out of the coil in this time. Hence the *rate* at which lines thread through or cut the secondary is perhaps 1000 times as great at break as at make, and therefore the electromotive force is also something like 1000 times as great.

If a closed circuit be dealt with then the induced electromotive force will depend on the change in the flux through the circuit. If ϕ_1 represents the flux at the beginning and ϕ_2 the flux at the end of the time interval t then

$$E = -\frac{\phi_2 - \phi_1}{t} \text{ (in abvolts)}$$

or

$$E = -\frac{1}{10^8} \cdot \frac{\phi_2 - \phi_1}{t} \text{ (in volts)}$$

where E is the average electromotive force during the time t. The minus sign is used to indicate the

direction of the induced electromotive force in accordance with Lenz's law.

If the instantaneous value of the electromotive force is required instead of the average, it is necessary to take but a very small interval of time, dt, at the instant in question and to make the corresponding small change in the flux and then

$$E = -\frac{d\phi}{dt} \text{ (in abvolts)}$$

If ϕ refers to the flux through a coil of one turn, then if there are n turns in the coil, obviously the induced electromotive force will be given

$$E = -n\frac{\phi_2 - \phi_1}{10^8 t} \text{ (in volts)}$$

This brief physical exposition will suffice to show how greatly the voltage of the induced current increases out of proportion to the shifting of the relative positions of the secondary and primary coils in terms of linear distance. The absolute voltages obtained with the inductorium employed in the author's experiments with a dry cell of 1.6 volts in the primary for some of the positions were as follows:

12 cm.—100 volts		6 cm.— 810 volts
10 cm.—105 volts		5 cm.—1223 volts
8 cm.—184 volts		4 cm.—1932 volts
7 cm.—368 volts		3 cm.—2400 volts

Figures were similarly obtained for the voltages at other positions, and a curve was plotted from which the approximate voltage for various pain thresholds could be easily interpolated. The calibrations of the induction coil were made with an R. C. A. cathode ray oscillograph.

It must be borne in mind that such a curve represents only the *peak* voltages of very short duration obtained at the *break* of the interrupting hammer. On superficial thought the high voltages obtained when the secondary is brought close to the primary coil may appear dangerous. From the physiological point of view, however, this is not the case. The fine electrodes are but a few millimeters apart and applied only to the *surface* of the skin. In the second place, the electric shock or stimulation depends not alone on the electromotive force but also on amperage or, in other words, on quantity of current. While the electromotive force may be greatly potentiated in such experiments as are described in this paper, the time of each break of the interrupter is extremely short, about 0.0001 of a second, and the current is so small that no other harmful effect·than an instantaneous sensation of pain is produced by application of the electrodes to the surface of the body.

For accurate determinations of pain thresholds, the authors employ a standardized method of procedure. The assistant holds the rat firmly yet gently and the testes are pushed down so as to dis-

tend the scrotum. In warm weather the pendulous testes are fully distended but in cold weather it may be necessary to press the lower part of the abdomen gently to distend the scrotum. The surface to which electrodes are to be applied is first wiped with a wad of cotton dampened with physiological saline. It is most important that the electrodes be always applied to the same points in any one experiment because the threshold of pain, while constant for any two given points, varies with different sensory points on the integument. It is therefore advisable to mark the spot tested in some convenient way.

DRUGS INVESTIGATED

Employing the method described in detail above, the writers tested a large number of drugs for their effect on the threshold of pain in the rat. Among the drugs thus studied were various opiates; a series of coal-tar analgesics such as acetanilid, acetphenetidin, acetyl salicylic acid, phenyl-salicylate, sodium salicylate; alcohol in various dosages; antipyrin, amidopyrin, various barbiturates, urethane, bromides and different alkaloids, some of which were suspected of being sensitizers rather than depressants of the pain threshold. The results obtained with some of these drugs are exhibited in the subjoined tables. Except in case of cobra venom and morphine, the data exhibited therein have been obtained by the use of different rats because the purpose of the present paper is to show primarily the accuracy of the rat-pain-threshold method in testing individual drugs. For comparing the effects of two or more drugs, however, it is desirable, of course, to test them on the same animals on different days. This was done specifically in connection with a comparative study of the analgesia effected by morphine and cobra venom, respectively.

To avoid any ambiguity of expression, it is well to stress the sense in which certain terms are employed in the present exposition. *Pain threshold* is the smallest electromotive force required to pro-

duce at a given point sufficient pain to elicit a squeal. When it is stated that the pain threshold is *raised*, it is meant that the secondary has been pushed to within fewer centimeters of the primary coil which, of course, denotes that more energy, more electromotive force in volts is required to elicit pain; hence it indicates analgesia. When the pain threshold is said to be *lowered*, it means that the secondary has been moved some centimeters farther away from the primary coil, and that consequently less energy and electromotive force are required to elicit the first sensation of pain. The animal has therefore become more sensitive.

Effect of Opiates on Threshold of Pain.—The effect of opiates on the threshold of pain is shown in Table I. The opium derivatives examined were morphine sulfate, codeine hydrochloride, heroin, papaverin, pantopon and dilaudid. The table exhibits the dose of the alkaloids injected, and the normal threshold expressed both in centimeters to indicate position of the secondary coil, and in volts. Succeeding columns in the table show any change obtained in pain threshold thirty minutes after, two hours after and, in some cases, four hours after injection of the alkaloids. It will be seen that all the opiates in sufficient doses effected analgesia; *i. e.*, raised the threshold of pain. However, small doses (*e. g.*, 1 mg. of morphine) often had no such effect.

Effect of Other Drugs on Threshold of Pain.— Table II shows the threshold for pain before and after injection of various other analgesics. It will be noted that when *small* doses of *alcohol* (1 cc. of a 5 per cent solution) were injected intraperitoneally, *no analgesia was produced*, as indicated by no change in the pain threshold. Similarly, 2 cc. of a 5 per cent solution produced no alteration. When large doses of alcohol or 10 cc. of a 5 per cent solution, however, were injected into a rat, complete unconsciousness and coma ensued. In such cases, as might have been expected, there was a general anesthesia and the pain threshold, of course, was abolished.

Table I.—Effect of Opiates on Pain Threshold of Rat

Rat No.	Drug Administered	Dose in Mg.	Normal Cm.	Normal Volts	15 to 30 Minutes after Dose Cm.	15 to 30 Minutes after Dose Volts	1 to 2 Hours after Dose Cm.	1 to 2 Hours after Dose Volts	Four Hours after Dose Cm.	Four Hours after Dose Volts
1	Morphine sulf.	1	8.0	185	7.6	250	7.8	218	...	...
2	Morphine sulf.	1	6.5	575	6.0	809	6.5	575	...	...
3	Morphine sulf.	1	6.4	630	6.6	530	7.4	280	...	...
4	Morphine sulf.	1.5	7.6	250	6.6	530	7.1	350	7.7	232
5	Morphine sulf.	2.0	7.5	265	6.1	770	7.0	368	7.6	250
6	Morphine sulf.	3.0	7.1	350	5.4	1080	5.8	953	7.7	232
7	Morphine sulf.	4.0	7.0	368	5.6	1018	5.7	983	7.0	368
8	Morphine sulf.	5.0	8.1	180	4.2	1755	0	2852	7.8	218
9	Codeine HCl	2	9.5	125	8.2	176	9.5	125	...	...
10	Codeine HCl	3	8.0	185	7.6	250	8.0	185	...	...
11	Codeine HCl	6	7.0	368	5.0	1223	7.0	368	7.0	368
12	Heroin	3	9.0	100	2.0	2576	2.0	2576	Recovered overnight	...
13	Papaverin HCl	2	7.7	232	7.2	325	7.2	325	7.2	325
14	Papaverin HCl	5	6.8	445	6.3	665	6.8	445	7.6	250
15	Pantopon	2	8.0	185	6.5	575	7.3	300	7.6	250
16	Pantopon	2	8.2	176	7.2	325	7.4	280	8.0	185
17	Dilaudid	0.25	9.0	100	7.0	368	7.0	368	...	...
18	Dilaudid	1.0	7.0	368	4.5	1530	4.8	1330	...	...

Table II.—Effect of Other Drugs on Pain Threshold of Rat

Rat No.	Drug Administered	Dose		Normal Cm.	Volts	15 to 30 Minutes after Injection Cm.	Volts	One Hour after Injection Cm.	Volts	Two Hours after Injection Cm.	Volts
1	Acetanilid	4	mg.	7.8	218	7.8	218	7.0	368	7.5	265
2	Alcohol, 5%	10	cc.	8.0	185	Coma	...	...	...	...	...
3	Alcohol, 5%	2	cc.	8.0	185	8.0	185	8.0	185	...	...
4	Alcohol, 5%	1	cc.	8.5	166	8.5	166	8.5	166	...	...
5	Antipyrin	10	mg.	7.6	250	...	...	7.2	325	7.3	300
6	Atropine sulf.	2	mg.	8.0	185	8.4	170	8.4	170	...	...
7	Barbital Na	10	mg.	8.3	173	...	...	...	...	7.0	368
8	Bromide Na	10	mg.	8.0	185	8.0	185	8.5	166	8.5	166
9	Bromide Na	20	mg.	8.6	162	8.6	162	8.3	173	8.3	173
10	Caffeine	4	mg.	8.1	180	8.1	180	8.4	170	...	...
11	Caffeine	8	mg.	8.2	176	8.2	176	8.3	173	...	...
12	Cocaine HCl	1	mg.	8.0	185	8.1	180	8.1	180	...	...
13	Cocaine HCl	2	mg.	9.5	125	9.8	110	9.8	110	...	...
14	Gynergen	0.2	mg.	8.2	176	8.2	176	8.2	176	8.2	176
15	Phenobarbital Na	5	mg.	7.4	280	...	...	7.8	218	7.7	232
16	Phenobarbital Na	10	mg.	9.0	150	...	...	7.7	232	...	...
17	Quinine sulf.	25	mg.	7.8	218	...	...	7.0	368	7.4	280
18	Salicylate Na	10	mg.	7.2	325	6.8	445	6.8	445	...	...
19	Strychnine nitr.	0.1	mg.	7.3	300	8.0	185	8.2	176	...	...
20	Urethane	40	mg.	7.4	280	...	...	8.0	185	8.2	176

Doses of 5 mg. of the barbiturates, sodium barbital and phenobarbital, effected little or no change in the pain threshold, while larger and toxic doses (10 mg.) definitely lowered it. No analgesia was produced by administration of even 40 mg. of urethane. From the pharmacological standpoint these findings with the barbitals and urethane are of considerable interest because they agree with clinical experience. These drugs are not real analgesics. The rational clinician does not employ the true hypnotic drugs in therapeutic doses for relief of pain but restricts their use to induction of sleep.

Caffeine did not raise the pain threshold; on the contrary, it tended to lower the pain threshold and rendered the rats more excitable. Similar findings were made after injection of small doses of strychnine. Gynergen, recommended by some for relief of migraine, did not raise the threshold of pain. This finding does not argue against its therapeutic efficiency in treatment of migraine but does indicate that the drug exerts an action other than that directly concerned with analgesia.

Of special interest were the data obtained with cocaine. This most potent of local anesthetics is well known to be a delirifacient when given by parenteral or intravenous injection. When cocaine hydrochloride was injected locally between the skin layers of the scrotum so as to produce a wheal, it exerted a powerful and long-enduring local anesthesia, as revealed by electrical stimulation. When the cocaine was injected intraperitoneally or subcutaneously, however, it definitely excited the animal, and the threshold of pain, instead of being raised, was actually lowered.

Threshold of Pain after Administration of Drugs by Stomach.—In Table III are exhibited the effects of various drugs, administered to rats by a special stomach tube. Some of the drugs studied in this connection, such as acetphenetidin and acetyl salicylate, for instance, could not be conveniently injected into the animals. Others, such as morphine and pantopon, are well known to relieve pain whether given by injection or *per os*. It will be noted that while morphine and pantopon administered by stomach tube raised the threshold of pain markedly, indicating the analgesia produced by these narcotics, cobra venom, the new analgesic, introduced in place of morphine for control of pain, effected no alteration of threshold of pain after oral administration. This drug acts only when injected intravenously or parenterally.

Comparison of Cobra Venom and Morphine.—Inasmuch as the use of cobra venom in place of morphine for the relief of pain is rapidly extending, a special study was made of these two medicaments (6, 7, 8, 9, 10, 11, 12). In Table IV are shown the results of a comparative study of morphine and cobra venom. Both drugs were injected intraperitoneally and the dosages employed—1 mg. of morphine and $\frac{1}{2}$ a mouse unit of cobra venom,

Table III.—Effect of Various Analgesics Given by Stomach Tube on Pain Threshold of Rat

Rat No.	Drug Administered	Dose Given	Normal Cm.	Volts	45 Minutes after Administration Cm.	Volts	2 Hours after Administration Cm.	Volts	3 Hours after Administration Cm.	Volts
1	Morphine sulf.	6 mg.	8.4	170	6.8	445	7.1	350	8.4	170
2	Pantopon	2 mg.	8.5	166	8.5	166	7.4	280	7.4	280
3	Cobra venom	5 m. u.	8.6	162	8.6	162	8.4	170	8.6	162
4	Acetphenetidin	30 mg.	8.8	155	7.5	265	7.6	250	...	...
5	Acetyl salicylic acid	30 mg.	9.3	135	9.2	140	9.6	120	...	...
6	Phenyl salicylate	30 mg.	7.2	325	7.5	300	7.2	325	7.2	325
7	Amidopyrin	30 mg.	7.6	250	7.5	265	6.0	809	Dead next day	...

Table IV.—Comparison of Cobra Venom and Morphine

Rat No.	Drug Administered	Dose	Normal		45 Minutes after Injection		2 Hours after Injection		4 to 5 Hours after Injection	
			Cm.	Volts	Cm.	Volts	Cm.	Volts	Cm.	Volts
1	Morphine sulf.	1 mg.	6.0	809	6.1	770	7.0	368	6.0	809
2	Morphine sulf.	1 mg.	6.4	630	6.6	530	7.4	280	6.4	630
3	Morphine sulf.	1 mg.	6.5	575	6.0	809	6.0	809	6.5	575
4	Morphine sulf.	1 mg.	8.0	185	7.2	325	7.2	325	8.0	185
5	Cobra venom	0.5 m. u.	7.0	368	6.6	530	6.7	480	6.5	575
6	Cobra venom	0.5 m. u.	8.3	173	7.5	265	7.2	325	7.2	325
7	Cobra venom	0.5 m. u.	8.3	173	6.8	445	6.3	665	6.2	715
8	Cobra venom	0.5 m. u.	7.2	325	6.5	575	6.1	770	6.0	809
9	Morphine sulf.	3 mg.	7.9	205	4.9	1260	8.0	185	7.9	205
10	Morphine sulf.	3 mg.	7.1	350	5.4	1080	7.9	205	7.2	325
11	Morphine sulf.	3 mg.	8.5	166	6.5	575	8.4	170	8.4	170
12	Morphine sulf.	3 mg.	8.0	185	6.8	445	8.3	173	8.0	185
13	Cobra venom	1 m. u.	8.0	185	7.0	368	4.0	1932	5.0	1223
14	Cobra venom	1.5 m. u.	8.2	176	8.4	170	7.2	325	6.4	630
15	Cobra venom	1.5 m. u.	7.1	350	6.8	445	6.8	575	5.8	953
16	Cobra venom	2 m. u.	8.0	185	6.0	809	5.4	1080	6.4	630
17	Cobra venom	0.5 m. u.	8.0	185	8.1	180	7.5	265	...	...
18	Cobra venom	0.5 m. u.	9.0	150	8.2	176	7.7	232	...	...
19	Cobra venom	0.5 m. u.	8.9	153	7.5	265	7.7	232	...	...
20	Cobra venom	2 m. u.	8.0	185	7.0	368	6.8	445	6.8	445

respectively—roughly corresponded to the relative therapeutic dosage of the two drugs in human subjects. Thus, where $1/8$ of a grain or 8 mg. of morphine are administered to a patient, the usual therapeutic dose of cobra venom would be 5 mouse units. The doses employed in the experiments described in this paper, 1 mg. of morphine sulfate and a $1/2$ mouse unit of cobra venom, respectively, bear the same ratio as the therapeutic dosage for man of $1/8$ of a grain of the former and 5 mouse units of the latter. Similarly 3 mg. of morphine would correspond to 1.5 mouse units of cobra venom. The table reveals that the 1 mg. of morphine produced very little analgesia in some rats and but a mild analgesia in others. On the other hand, $1/2$ a mouse unit of cobra venom solution always effected considerable analgesia or increase in pain threshold. While the analgesia produced by morphine is prompt in onset, it generally disappears in a few hours. Cobra venom analgesia, on the contrary, is slow in onset but, once effected, lasts much longer than that of morphine. These experimental findings agree with numerous clinical experiences described elsewhere by the senior author. A partial explanation at least of this striking difference between morphine and cobra venom is supplied in his report of studies on the activity of brain oxydases as influenced by the respective drugs (13).

COMMENT

The present writers describe a new method for quantitative comparison of the analgesia effected by various drugs, which consists of determining the pain threshold for selected points on the scrotum of the adult male rat by means of the faradic stimulus of calibrated induction coil. It was found that the normal pain threshold for any given point on the scrotum of the rat is constant for many hours and can be expressed in absolute physical units. The threshold of pain for selected points on the sensitive scrotum of the normal test animals having been determined, it was also measured for the same points on the same animals after various drugs had been administered by stomach tube. In this way various opium alkaloids were compared with regard to their analgesic action on the rat, and a series of other analgesics and control drugs were examined. The new method has also proved useful in differentiating a purely local anesthetic from a general analgesic action. Thus it was shown that, although cocaine is a powerful local anesthetic, injections of this drug or its salts produced excitement and lowered the pain threshold, i. e., rendered the animals more sensitive. A special comparative study was made of morphine and cobra venom and it was found that both these drugs, when injected in rats, increased the threshold of pain, that is, necessitated an increase of electric stimulation to elicit the first sensation of pain. When the two drugs were given by stomach, a similar effect was produced by morphine but not by cobra venom. A striking difference was noted between the two drugs with regard to time of onset, on the one hand, and duration of their analgesia, on the other. That of morphine was rapid in onset and short in duration. The analgesia of cobra venom,

however, was very slow in onset and of much longer duration. These experimental findings are in complete agreement with numerous clinical data gathered concerning this drug by the senior author.

SUMMARY

1. A new method for quantitative determination of pain threshold in experimental animals has been described.

2. The method consists of applying the faradic current from a standardized induction coil to certain sensitive areas of the scrotum of tame adult male rats and measuring in absolute physical units the minimal energy required to elicit a painful squeal, i. e., the threshold of pain.

3. In complete agreement with clinical experience, a large number of drugs examined in this way were found to produce analgesia in the rat, a circumstance recommending use of this new method in research concerning the analgesia produced by unknown substances.

4. A large number of analgesic drugs (opiates, coal-tar derivatives, alkaloids, etc.), tested in this way, have yielded data running parallel to clinical experience with some medicaments in men.

5. The findings obtained by such a method in studying analgesia produced by morphine and cobra venom agree not only with those derived from studies on guinea pigs and on *normal* human subjects, but also with those obtained from numerous clinical reports.

6. The new method offers a useful and accurate means of detecting analgesic properties of new compounds on which investigative work has not progressed so far as to warrant a clinical trial on human subjects.

BIBLIOGRAPHY

(1) Macht, D. I., Herman, N. B., and Levy, C. S., *Proc. Nat. Acad. Sci.*, 1 (1915), 582–585.

(2) Macht, D. I., Herman, N. B., and Levy, C. S., *J. Pharmacol.*, 8 (1916), 1–37.

(3) Kronecker, "Arbeiten aus der physiologischen Anstalt zu Leipzig" (1871), 186.

(4) Macht, D. I., *Compt. rend. soc. biol.*, 120 (1935), 286–289.

(5) Macht, D. I., *Proc. Nat. Acad. Sci.*, 22 (1936), 61–71.

(6) Macht, D. I., *Ann. Int. Med.*, 11 (1938), 1824–1833.

(7) Macht, D. I., *M. Press*, 201 (1939), 254–257.

(8) Rottmann, A., *Klin. Wochschr.*, 16 (1937), 1051–1056.

(9) Klobusitzky, D., *Ibid.*, 16 (1937), 569–575.

(10) Chopra, R. N., and Chowhan, J. S., *Indian Med. Gaz.*, 72 (1937), 339–348.

(11) Bullrich, R. A., *Rev. argent. de cardiol.*, 3 (1936), 111–120.

(12) Lavedan, J., *Paris méd.*, 1 (1935), 221–227.

(13) Macht, D. I., and Bryan, H. F., *Compt. rend. soc. biol.*, 123 (1936), 385–388.

A Pharmacognostical Study of Serenoa Serrulata (Saw Palmetto)[*],[†]

By B. V. Christensen[‡] and R. C. Stokes[**]

COLLECTION

Information in the literature on the collection of Saw Palmetto berries is questionable and often contradictory. Statements have been made that the time of collection extends from August to January, or even rarely to March (5). Others say that the berries ripen in October and November and may be found until the middle of December (4). Questionable statements regarding the methods of collection are prevalent. For example, the United States Dispensatory (6) states that the fruits are gathered when fully mature, partially dried artificially and packed in barrels, and that, to the contents of each barrel, a small amount of alcohol is added as a preservative.

In order to learn more exactly the time of collection of the berries and to obtain accurate information concerning the methods of collection, several trips were made by the writers to localities in Florida from which the commercial supply of Saw Palmetto berries