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THE ROLE OF EPINEPHRINE IN ANALGESIA *

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THE potent analgesic agents, morphine, codeine and demerol, have been assumed to exert their pain-relieving action through a depression of the thalamic region of the central nervous system. The use in various laboratories of improved methods for measuring analgesia, however, has revealed several indications that the autonomic nervous system may also be involved in the production of analgesia. These indications are: the potentiation of opiate analgesia by neostigmine (1), the production of analgesia by epinephrine (2) and other vasopressor amines (3), the production of analgesia by neostigmine and physostigmine (4), and the observation that the cholinergic depressants, scopolamine and atropine, tend to decrease both the intensity and duration of analgesia (5).

Recently, Harris and Friend (6) have reported that adrenalectomized rats showed less analgesia from morphine than did normal rats. These authors also presented evidence that the medullary portion, rather than the cortical portion, of the adrenal gland is responsible for the decreased analgesia.

Slaughter and co-workers (1) suggested that acetylcholine plays some part in the potentiation of morphine analgesia by neostigmine, but did not explain the mechanism of action. There is good evidence that morphine (7) and acetylcholine (8) stimulate the adrenal gland. This action of morphine may be either direct or through an inhibition of cholinesterase. Thus the potentiating action of neostigmine in

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opiate analgesia may be an indirect action in causing an increased output of epinephrine. It would appear, then, that epinephrine may be a basic factor in analgesic action. If this hypothesis is correct, then analgesic drugs must stimulate the production of epinephrine either through a direct effect on the adrenal gland or indirectly through inhibition of cholinesterase activity or both. Homer Smith (9), in his 1939 Harvey lecture, listed a number of agents that stimulate the adrenal gland and among these are morphine, chloroform and ether. It is also known that pain itself can cause an analgesia which persists for some time after the source of pain has been removed (10). This has been explained as being due to release of epinephrine.

In this paper a report is made of extensive studies conducted in this laboratory during the last two years on the pain thresholds of both human beings and normal and adrenalectomized dogs as they are influenced by drugs having a bearing on this problem.

PROCEDURE

All the analgesic measurements were made by the Wolff, Hardy and Goodell method (11). A machine built by the Experimental Engineering Laboratories was used for the human experiments. The end point used was the sudden "welling up" of pain at the end of the three-second interval. Volunteer medical students were used as subjects. The animal experiments were made with a Wolff-Hardy apparatus built in this laboratory and the skin fleck as described by Andrews and Workman (12) was used as the end point. This method has been used in this laboratory with consistent results for the past several years. The adrenal glands were removed by a two-stage operation and the dogs were maintained by daily injections of desoxycorticosterone acetate.

RESULTS

Human Subjects.—The effects of atropine, scopolamine and neostigmine on the pain thresholds of human beings have been published in another paper (5). Atropine and scopolamine tended to decrease the analgesic action of morphine, demerol and methadone,* while neostigmine not only increased the analgesic action of these agents (1, 5), but was capable of producing analgesia when administered alone (4, 5). All data are expressed as percentage deviations from the normal pain threshold.

Figure 1 shows the effect of the subcutaneous administration of graded doses of epinephrine and of a combination of neostigmine and epinephrine. The duration, but not the intensity, of the analgesia seems to vary roughly with the dose of epinephrine. Neostigmine tended to increase the intensity and duration of the analgesia produced by 0.4 mg. of epinephrine. It was observed that there was a period of about

* Supplied by the Abbott Laboratories, N. Chicago, Illinois.

twenty minutes following the rise in pain threshold in which the subjects experienced a hypersensitivity of 2 to 5 per cent. When the effects of analgesic agents such as morphine or methadone were followed to completion there was also a period of hypersensitivity.

The effect of d-amphetamine* on the pain threshold was determined in order to test the action of another vasopressor agent. The activity of 10 mg. of d-amphetamine given subcutaneously is represented in

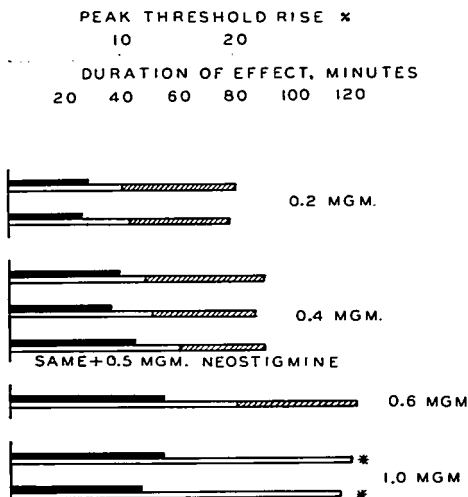


FIG. 1. The effect of subcutaneous injection of epinephrine on the pain threshold. Solid line = peak threshold rise; open lines = total duration of pain threshold rise. Cross hatched lines = the period of time when subjects were hypersensitive. * Hypersensitivity present, but its duration not followed.

figure 2. It will be noted also from this figure that neither atropine nor scopolamine affected the intensity of the analgesia. In the subject to whom scopolamine was given the duration was slightly longer, but this undoubtedly was due to the fact that absorption was retarded since the peak was delayed.

Parson and Goetzl (10) have demonstrated that pain itself produces analgesia which persists even after the perception of pain subsides—an action they ascribe to release of epinephrine. These findings were confirmed in this laboratory. Figure 3 shows the effect of ischemic pain produced by the application of a blood pressure cuff at

* Supplied as Dexadrine by Smith, Kline and French, Philadelphia, Pa.

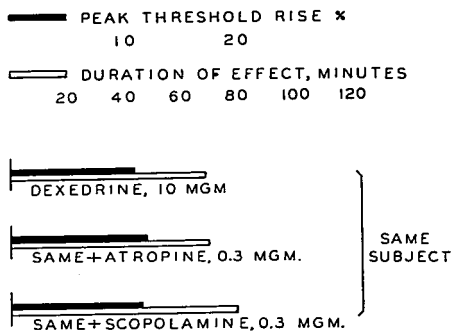


FIG. 2. The peak pain threshold rise and duration of rise when dexedrine alone and dexedrine with either atropine or scopolamine are given subcutaneously. Solid line = the percentage peak of threshold rise; open lines = duration of threshold rise. Same subject used for each experiment.

180 mm. of mercury for ten minutes. The average curve for three subjects is presented so that the time relationships can be observed.

Since both epinephrine and d-amphetamine produced analgesia, it seemed advisable to study the effect of an agent causing vasodilatation. Figure 4 represents the effect of nitroglycerine on the analgesia produced by 10 mg. of d-amphetamine given either subcutaneously or intra-

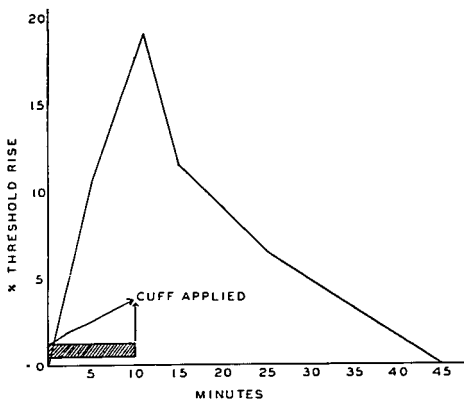


FIG. 3. Effect of ischemic pain on the pain threshold rise. Blood pressure cuff applied for ten minutes at 180 mm. of mercury. The curve represents the average percentage rise of 3 subjects.

venously. Blood pressure recordings, taken very rapidly after each threshold determination, are indicated on the chart in the case of the intravenous experiment. In three subjects 0.4 mg. of nitroglycerine alone, given sublingually, produced readings 2 to 5 per cent below the normal pain threshold of the subjects and persisting for ten to twenty minutes.

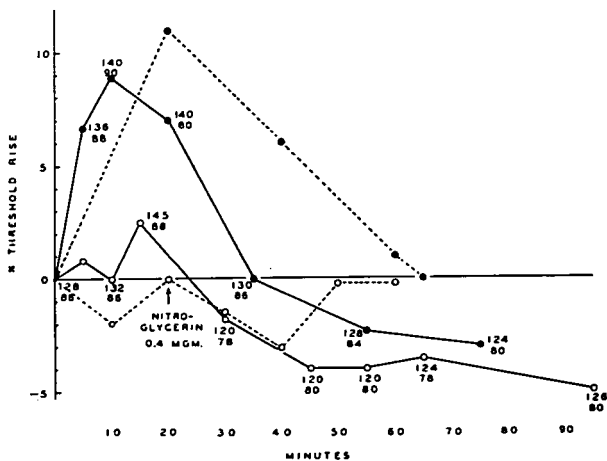


FIG. 4. The curves represent the pain threshold rise of dexedrine and dexedrine followed by nitroglycerin.

- = Dexedrine, 10 mg. intravenously.
 - = Same, with nitroglycerin 0.6 mg. given sublingually.
 - = Dexedrine 10 mg. subcutaneously.
 - = Same with nitroglycerine 0.4 mg. sublingually, followed in twenty minutes by 0.4 mg. more of nitroglycerine.
- Same subject used for all experiments. Numerals represent blood pressures.

Figure 5 represents the effect on two subjects of nitroglycerine administered in one instance forty minutes and in the other fifty minutes after a subcutaneous dose of methadone. It will be noted that there was a prompt fall in threshold to a subnormal level, followed by a rise and then a second fall. The total duration of the analgesic effect was greatly shortened from the normal.

To determine whether atropine and nitroglycerin would influence analgesic agents other than the narcotics, 25 per cent nitrous oxide was administered to two subjects. Figures 6 and 7 show the effect of nitroglycerine and atropine on the analgesia produced by this agent. Atropine practically abolishes the pain threshold rise and nitroglycer-

ine completely abolishes the analgesia for a period of about twelve minutes. Similar results were obtained with 3 per cent cyclopropane. Further studies of this nature on the general anesthetic agents are now in progress. It should be emphasized that concentrations of the anesthetics were used with which the subject retained his faculties. When higher concentrations of these agents were used the subject was no longer capable of judging the pain threshold. The same statement can be made concerning the use of the other analgesic agents when dosages were purposely kept low to eliminate marked sedative effects.

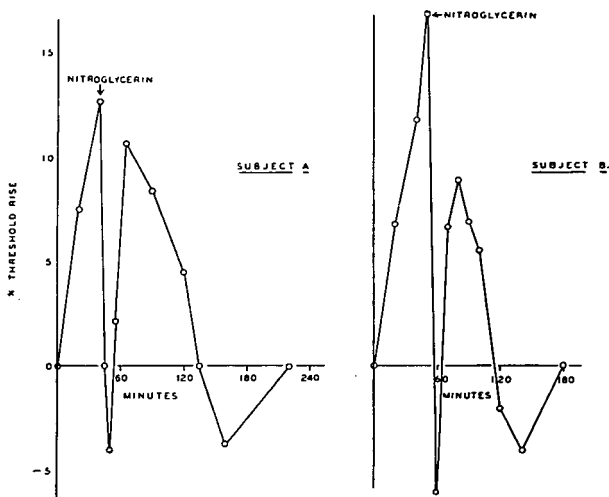


FIG. 5. The curves represent the effect of 0.6 mg. of nitroglycerin given sublingually on the pain threshold rise of 5 mg. of methadone given subcutaneously. The nitroglycerine was administered forty minutes after the methadone in subject A and fifty minutes after in subject B.

Dogs.—Several normal animals were used to determine the pain threshold rise of three analgesic drugs, namely, morphine, demerol and methadone. These drugs were administered intraperitoneally and the effect on pain threshold determined at fifteen-minute intervals. Percentage changes in pain thresholds for 9 normal dogs are recorded in table 1.

Five dogs were selected from this normal group for removal of the adrenal glands. One animal was used eight days after the second operation; the others were not used until two weeks or longer had elapsed after the removal of the second adrenal gland. These animals

were all in a good state of nutrition. Table 2 represents the pain threshold changes for these animals when the three analgesic agents which were used in the normal animals were administered intraperitoneally. It will be observed that only slight rises were obtained, and that shortly after these rises, a hypersensitive period occurred. The results shown here are the average of several determinations on each animal. In about 50 per cent of these determinations no rise was elicited, and the total period was one of hypersensitivity. This was most prominent with methadone. Morphine usually produced some early rise before the period of hypersensitivity. The animals were more depressed by all of these drugs, but especially by morphine, than were the normal animals. It was difficult to obtain consistent responses during the first thirty minutes from the animals given morphine.

TABLE 2
ADRENALECTOMIZED DOGS

Drug	mg./kg.	Time in Minutes After Intraperitoneal Injection										
		15	30	45	60	75	90	105	120	135	150	165
Morphine	1	4.7	4.7	1.3	0	-4.7	-5.2	-4.6	-3.2	0		
Demerol	8	2.1	2.1	2.4	-2.4	-4.0	4.4	-2.0	0			
Methadone	1	0	-10.0	-12.0	-12.0	-10.0	-7.0	-7.0	-5.0	-5.0	0	0
Methadone	2	3.7	-4.6	-8.1	-3.3	-2.8	-2.8	-1.0	0	-3.0	0	0

TABLE 3
AVERAGE PERCENTAGE PAIN THRESHOLD RISE FOLLOWING THE ADMINISTRATION OF
0.05 MG./KG. OF NEOSTIGMINE INTRAMUSCULARLY

	Time in Minutes After Intraperitoneal Injection										
	15	30	45	60	75	90	105	120	135	150	165
Normal	12.3	12.3	17.5	16.4	12.0	8.0	8.0	8.0	4.0	4.0	.0
Adrenalectomized	0.0	-5.1	-8.7	-5.1	-7.1	0	-2.0	0	0	0	

Table 3 represents the average rise in pain threshold of 7 normal animals and of 3 of the operated dogs when 0.05 mg. per kilogram of neostigmine was administered intramuscularly. In 2 normal animals 0.5 mg. per kilogram of atropine given intramuscularly five minutes before neostigmine prevented any rise in pain threshold. A dosage of 0.25 mg. per kilogram of atropine did not completely abolish the neostigmine effect on pain threshold. It will be observed that neostigmine did not produce a rise in pain threshold after adrenalectomy, indicating that its action must be through the adrenal gland.

To determine whether other cholinesterase-inhibiting agents would also produce analgesia, diisopropylfluorophosphate (DFP)* was se-

* Supplied by Merck & Co., Rahway, N. J.

lected for study. Table 4 represents the average effect on pain threshold of 5 normal dogs and 2 of the operated animals. The DFP was suspended in oil and 0.1 mg. per kilogram was administered intramuscularly. None of the normal animals were followed beyond four hours as the analgesia seemed to persist for a long period. Following adrenalectomy no pain threshold rise could be demonstrated and there was a period of hypersensitivity.

TABLE 4
AVERAGE PERCENTAGE PAIN THRESHOLD RISE FOLLOWING THE ADMINISTRATION OF
0.1 MG./KG. OF DFP INTRAMUSCULARLY

	Time in Minutes After Intraperitoneal Injection										
	15	30	45	60	75	90	105	120	135	150	165
Normal	6.4	16.9	22.0	26.1	29.8	29.8	29.8	25.7	23.0	21.7	21.5
Adrenalectomized	0.0	-3.0	-4.3	-7.2	-6.1	-1.1	-3.4	-1.0	0	-2.0	0

It was demonstrated that epinephrine and d-amphetamine were capable of producing a rise in the pain threshold of human subjects. d-Amphetamine and epinephrine also produce pain threshold rises in dogs. To determine whether other vasoconstricting agents would alter the pain threshold, 10 units of pitressin was given intramuscularly to dogs before and after adrenalectomy. The average peak rise of the pain threshold was 9.7 per cent in the normal and 8.9 per cent in the operated animals. Chemical evidence of increased epinephrine following analgesia has not been demonstrated; in fact, it is doubtful whether epinephrine can be detected in the venous blood. The method of Bloor and Bullen (13) was used in an attempt to determine blood epinephrine during analgesia. No alteration in the catechol substances could be determined. The blood samples were taken twenty and sixty minutes after a dose of 2 mg. per kilogram of morphine. Because of the failure to demonstrate any increase in catechol substances in these animals, 0.5 mg. of epinephrine was injected subcutaneously into 2 human subjects and blood was drawn ten minutes and thirty minutes after the injection. It was not possible to detect any increase in catechol substances. Such amounts of epinephrine injected into human subjects (see fig. 1) produce significant rises in pain threshold.

Recently, Nickerson and Goodman (14) have reported that dibenamine reverses the normal vasopressor effect of epinephrine. In our laboratory 2 normal dogs were given intravenously 20 mg. per kilogram of dibenamine. Both of these animals gave somewhat greater pain threshold rises than normal with methadone. In the light of the experiments thus far reported it is difficult to explain the elevation of threshold with this drug. Dogs receiving this amount of dibenamine exhibit a normal blood pressure, but it would seem logical to assume that if all the body epinephrine were reversed, dogs treated with this

agent should exhibit a lowered blood pressure. Until more is known about the epinephrine reversal reaction, too much importance need not be ascribed to the failure of dibenamine to reverse the analgesia of methadone.

An interesting observation was made in the reaction of the operated animals to epinephrine. Two of the animals were given 1 mg. of epinephrine intramuscularly. These animals became very tense and excited and no analgesia determinations could be made. Both of these animals died some ten hours later. Normal animals tolerated this amount of epinephrine and showed a substantial rise in pain threshold.

DISCUSSION

From the results presented, it appears that analgesic agents exert at least part, but probably not all, of the analgesic effect through a common intermediary, namely epinephrine. Sedation of the central nervous system must also play an important role. It is well known that the barbiturates are practically devoid of analgesic action, but if the sedation becomes sufficient, analgesia does occur.

It appears from the data presented that any agent which is capable of directly or indirectly stimulating the adrenal gland or of constricting blood vessels will exhibit pain-relieving activity. It is obvious, however, that all such agents would not be suitable analgesics; those producing stimulation of the central nervous system, such as amphetamine and ephedrine, would lack the concomitant sedative factor which apparently is important in analgesia.

It is not apparent at this time just how the analgesic agents stimulate epinephrine. While morphine (15, 16), demerol (17) and methadone (17) are cholinesterase inhibitors *in vitro*, it is not known whether this action is sufficient to play an important role *in vivo*. Several arguments may be presented to the effect that the cholinesterase inhibition is not the sole mechanism for stimulating the adrenal gland. First, atropine, in the dosage used, blocks the neostigmine threshold effect completely, but only partially inhibits that of the three analgesic agents. Second, according to Adriani and Rovenstine (18), nitrous oxide does not inhibit cholinesterase, although atropine blocks the analgesia of this agent more completely than it does that of such drugs as morphine or methadone. In support of the conception that the cholinesterase-inhibiting action is a part of the mechanism, the evidence that acetylcholine stimulates the output of epinephrine may be cited (8). Furthermore, the failure of atropine and scopolamine to block the analgesic action of another vasopressor agent (fig. 2) suggest that once the vasoconstriction has occurred, cholinergic depressants are no longer effective in decreasing analgesia. Also, agents which are potent cholinesterase inhibitors, namely neostigmine, physostigmine and DFP, produce analgesia, while the cholinergic depressants tend to inhibit analgesia when no direct vasopressor agents have been administered.

The position of epinephrine as an important intermediary agent in analgesia is supported by the evidence obtained from the 5 adrenalectomized dogs, and from the work of Harris and Friend (6). In all instances either a minor or no elevation of pain threshold was obtained when the three potent analgesics were injected. The intramuscular injection of 1 mg. of desoxycorticosterone did not alter the normal threshold. According to the concept of Langworthy (19) and others (20), the only action of the adrenergic system is a vascular one. The fact that a vascular dilatation, such as is produced by nitroglycerine, inhibits analgesia would make it appear that vascular changes influence the production of analgesia. It might be argued that by producing a vascular dilatation the thermal stimulus was "washed away." Two dogs were given subcutaneously 5 mg. per kilogram of morphine, and the animals' ears were tested for sensitivity to pinching and pricking. After thirty minutes the ears were quite insensitive to pinching and slow pin pricks. Both were given 0.4 mg. of nitroglycerine subcutaneously and during a period of about ten minutes both animals showed hypersensitivity as nearly as could be judged by these crude tests. Wolff, Hardy and Goodell (21) stated that epinephrine renders the human subject refractory to the pain threshold-raising action of morphine. In their experiments the epinephrine was administered two hours before the morphine—when blood pressure effects had subsided but the subjects were still "tense and excited." In the experiments in our laboratory the subjects experienced this tense and excited feeling for a considerable time after the initial pain threshold rise had disappeared. In fact, they experienced these symptoms more intensely during the hypersensitive period. In the experiments of Wolff et al. (21) their subjects may have been in a hypersensitive area of the epinephrine action and consequently there appeared a lower pain threshold for morphine. No experiments are recorded wherein the two drugs were administered simultaneously. Ivy et al. (2) have demonstrated that ephedrine definitely potentiates the action of morphine when they are given together.

Ivy, et al. (2) further concluded that the analgesic action of epinephrine is the result of a specific action of epinephrine on the pain-perceiving mechanism. If the epinephrine action is central, the mechanism of this action may well be through vascular changes. The fact that analgesic agents do not obtund sharp sudden pain as satisfactorily as they do dull steady pain, might point to a peripheral vasoconstriction which would impede the transmission of sensory impulses, perhaps along the smaller fibers which may carry the steady type of pain.

Burn (22), in a recent review of the action of epinephrine, assembled the literature relative to the influence of epinephrine on nerve fiber transmission. In his review he stated that small amounts of epinephrine facilitate passage of the impulse along nerve fibers, while larger amounts tend to inhibit or impede transmission. While he does

not completely explain the mechanism, his review does not necessarily preclude vascular changes along the nerve trunks as being the cause of these actions of epinephrine. During analgesia amounts of epinephrine may be produced sufficient to cause vasoconstriction of the smaller vessels, but not to cause observable changes in blood pressure. Morphine, demerol and methadone do not produce blood pressure changes. The after-effect of epinephrine on blood pressure is to produce a fall in pressure after the initial rise. This may account for the subnormal pain thresholds following administration of epinephrine or even after the analgesics themselves. Another explanation for the after-effects may be that acetylcholine itself overcomes any epinephrine effect and produces dilatation. At the present time it is difficult to offer any explanation of the hypersensitivity that develops in the adrenalectomized animals. It is believed that our results may establish that epinephrine plays a role in the mechanism of analgesia, and evidence appears that this may be a vascular effect. Perhaps the vascular effect results in a hypoxic state in the nerve tissue. The exact mechanism, however, by which a vascular change might bring about the analgesia, and the central or peripheral nature of the analgesia requires further experimentation.

The concept that epinephrine is an intermediary factor in analgesia may be challenged on the basis that the effects of epinephrine, such as rapid heart rate, dilated pupil, loss of intestinal mobility, and so forth, are not experienced with the analgesic agents. In most instances the adrenergic system is antagonized by the cholinergic system. Thus the usual symptoms of epinephrine may be counteracted by the cholinergic system, if the contention that this system is stimulated by analgesic drugs is correct.

SUMMARY

Adrenalectomy in dogs decreases the pain threshold response following administration of morphine, demerol and methadone.

Agents which inhibit cholinesterase produce analgesia.

Epinephrine and other vasopressor amines are analgesic but their analgesia is not inhibited by the cholinergic depressant drugs.

It is suggested that the mediation of epinephrine, possibly through a vascular effect, is an important component of the analgesic effect produced by the compounds studied.

REFERENCES

1. Slaughter, D. H., and Munsell, D. W.: Some New Aspects of Morphine Action Effects on Pain, *J. Pharmacol. & Exper. Therap.* 68: 104-112 (Jan.) 1940.
2. Ivy, A. C.; Goetzl, F. R.; Harris, S. C., and Burrill, D. Y.: The Analgesic Effect of Intracarotid and Intravenous Injection of Epinephrine in Dogs and Subcutaneous Injection in Man, *Quart. Bull., Northwestern Univ. M. School* 18: 298, 1944.
3. Ivy, A. C.; Goetzl, F. R., and Burrill, D. Y.: Morphine-Dextroamphetamine Analgesia: Analgesic Effects of Morphine Sulfate Alone and in Combination with Dextroamphetamine Sulfate in Normal Human Subjects, *War Med.* 6: 67-71 (Aug.) 1944.

4. Floodmark, S., and Wrammer, T.: The Analgesia of Prostigmin and Physostigmine, *Acta Physiol. Scandinav.* **9**: 88, 1945.
5. Christensen, E. M., and Gross, E. G.: A Comparison of the Analgesic Effects on Human Subjects of 6 Dimethyl Amino-4, 4-Diphenyl-3-Heptanone (AN 148), Morphine and Meperidine (Demerol) and the Relative Efficiency of AN 148 for Preoperative and Postoperative Use, *J. A. M. A.* (In press).
6. Harris, S. C., and Friend, F. J.: Contribution of Adrenals to Morphine Analgesia, *Federation Proc.* **6**: 124, 1947.
7. Houssay, B. A.; Lewis, J. T., and Molinella, E. A.: Etudes sur l'hyperglycemie consecutive a l'injection de morphine, *Role des surrenales, comp. rend. soc de biol.* **99**: 1408, 1928.
8. Feldberg, W.; Minz, B., and Trudzimura, H.: The Mechanism of the Nervous Discharge of Adrenaline, *J. Physiol.* **81**: 286, 1934.
9. Smith, Homer W.: Physiology of the Renal Circulation, The Harvey Lectures, p. 166, 1939.
10. Parson, C. M., and Goetzl, F. R.: Effect of Induced Pain on Pain Threshold, *Proc. Soc. Exper. Biol. & Med.* **60**: 327, 1945.
11. Wolff, H. G.; Hardy, G. D., and Goodell, H.: Studies on Pain, *J. Clin. Investigation*, **19**: 659-680 (July) 1940.
12. Andrews, H. L., and Workman, W.: Pain Threshold Measurements in the Dog, *J. Pharmacol. & Exper. Therap.* **73**: 99-103 (Sept.) 1941.
13. Bloor, W. R., and Bullen, S. S.: The Determination of Adrenalin in Blood, *J. Biol. Chem.* **138**: 727-739 (Apr.) 1941.
14. Nickerson, M., and Goodman, L. S.: Pharmacological Properties of a New Adrenergic Blocking Agent: N, N-Dibenzyl B. Chlor Ethylamine (Dibenamine), *J. Pharmacol. & Exper. Therap.* **89**: 167, 1947.
15. Bernheim, F., and Bernheim, M. L. C.: Action of Drugs on the Cholinesterase of the Brain, *J. Pharmacol. & Exper. Therap.* **57**: 427, 1936.
16. Slaughter, D. H., and Lackey, R. W.: Effect of Morphine Sulphate on the Serum Cholinesterase, *Proc. Soc. Exper. Biol. & Med.* **45**: 8, 1940.
17. Unpublished Data from this Lab.
18. Adriani, J., and Rovenstine, E. A.: The Effect of Anesthetic Drugs on Activity of Cholinesterase, *Anesth. & Analg.* **20**: 109-111 (Mar.-Apr.) 1941.
19. Langworthy, O. R.: General Principles of Autonomic Innervation, *Arch. Neurol. & Psychiat.* **50**: 590-602 (Nov.) 1943.
20. Hare, K.: Visceral Functions of the Nervous System, *Ann. Rev. Physiol.* **8**: 375-420, 1946.
21. Wolff, H. G.; Hardy, J. D., and Goodell, H.: Studies on Pain, *J. Clin. Investigation* **19**: 659-680 (July) 1940.
22. Burn, J. H.: The Relation of Adrenaline to Acetylcholine in the Nervous System, *Physiol. Rev.* **25**: 377-394 (July) 1945.