heart disease, when contrasted with normal subjects. A summary of the significant data is given in Table V.

Summary. The circulation time is characteristic for the subject rather than for the type of heart disease. On the average, the circulation time for individuals with heart disease is prolonged. The difference between the circulation time before and after 5 minutes of exercise is greater than that before and after a 5-minute period of rest. The difference between the circulation time before and after 5 minutes of exercise in the diseased group is similar to that of the normal group. The difference induced in the circulation time after exercise is not significant as a test of cardiac efficiency.

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Comparison of Different Types of Central Stimulation from Analeptics.*

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In a study of the analeptic potency of the sympathomimetic amines,[1] a simple and rapid method has been developed in this laboratory for graphic registration of one kind of central stimulation. In order to establish standards of comparison for this study, observations have been made on 5 unrelated analeptics, to determine whether the method will demonstrate differences between the various compounds, which could serve as a basis for analysis of their actions. The present report gives the results on the stimulant actions of metrazol, picrotoxin, coramine, caffeine, and cocaine, as revealed by this procedure. Later, results of the application of this same method to the sympathomimetic amines will be reported.

After testing a considerable variety of methods for measuring the total activity of animals, one was devised which utilizes well known principles, although somewhat differently applied. It has the advantage of graphically integrating total activity, without the necessity of laboriously measuring marks of a lever on a drum, as is done

* Supported, in part, by Grant 345 of the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association.

1 Tainter, M. L., Whitsell, L. J., and Dille, J. M., *J. Pharm. Exp. Therap.*, **1939, 67**, 56.

with the usual types of apparatus.[9] A white rat is placed in a small wire cage 6 inches square, which is suspended from a spring, and moves up and down in response to each movement, or shift in balance, of the animal. A suitable spring for this purpose is like that used in window blinds, since it is made of well tempered steel, does not change its elasticity, and has the proper degree of sensitivity for appropriate records. This movement is summated and recorded by connecting the spring to a Harvard work adder. With each revolution of the work adder, electrical contact is made through a mercury cup, recording on a kymograph through a signal magnet in the usual way. Twenty such units are used, with the cages suspended in a constant temperature chamber of 27 to 29°C, so the animals may be kept warm and at nearly basal conditions. The chamber is brightly lighted, since the rats are more quiet in the light than in darkness, their normal period of activity. Groups of 10 rats are used in each series, one-half being injected subcutaneously with normal saline solution (0.85% NaCl), and the other half with a test solution, and their activity recorded continuously until it returns to normal. One week later, the same rats are reinjected, with the groups reversed to give a "cross-over" test. Care is taken that each animal is put in the same cage, so that any differences in sensitivity of the individual recording units are balanced out by the method of controls used. This latter precaution does not appear to be particularly important since the apparatus is very uniform.

From the total values of the recorded movements observed in each half hour after the amines are injected there are subtracted the amounts of activity shown by the same animals after the salt solution injections. The net revolutions by the 10 rats are averaged to give the general curve of response to the dose in question. The dosages of the drugs used started from those which were completely ineffective, and increased by increments of 100% until ones were reached which caused convulsions or death. Since this is a severer reaction than is desirable for ordinary therapeutic use, it was not thought worthwhile, for the present study, to test larger ones.

The results are summarized graphically in Fig. 1.

It is clear that metrazol and picrotoxin behaved quite differently from coramine and caffeine. These former agents produced no significant increases in activity over the control levels, except when, with 40 mg of metrazol per kilo, 7 of the 10 rats had convulsions, and with 1.6 mg picrotoxin, 5 of the 10 rats showed the same response. However, no animals died in these 2 series. The convulsions resem-

[9] Shirley, M., *Psychol. Bull.*, 1929, **26**, 341.

bled those commonly ascribed to spinal and medullary stimulation. They lasted about 15 seconds for each seizure and recurred for 30 minutes. Thereafter the animals showed no more activity than the control spontaneous variations. It appears, therefore, that metrazol and picrotoxin do not increase the total activity of rats, as measured by this type of apparatus, unless convulsant or fatal doses are used.

On the other hand, coramine, caffeine, and cocaine presented quite a different picture. Twenty mg of coramine per kilo increased the activity only slightly above that of the control animals, with 40 mg there was a definite stimulation, and with 160 mg there was an increase up to 12 revolutions per hour, for about 7 hours. This latter dose caused convulsions in 2 rats. Similarly, caffeine showed what is probably a threshold response to 10 mg per kilo, and a very marked response of 22 revolutions per hour to 40 mg per kilo, with one fatality. Experiments with cocaine (not shown in Fig. 1) were carried out on 6 animals for each dose with similar results. Doses of 50 and 60 mg per kilo produced an increase of about 40 revolutions per half hour without the appearance of convulsions. Maximum activity was reached at the end of one hour, and activity returned to normal at the end of about 3.5 hours. One of the six rats died from 60 mg of cocaine.

The animals receiving coramine, caffeine and cocaine in effective doses showed a rather characteristic behavior. They moved constantly around the cage, rubbed their noses, scratched and gnawed at the meshed wire, in a continuous coördinated muscular activity of a type resembling that of a purposeful or psychic "drive". This was strikingly different from that of the convulsions of picrotoxin and metrazol, and was probably initiated from levels higher than the medulla.

A large body of published observations agree that caffeine in appropriate doses, can shorten reaction time, increase the speed of discrimination and other similar criteria of cortical activity.[2, 3, 4, 10] In addition, Miller and Miles[5] have shown that rats, injected with 50 mg per kilo of caffeine sodium benzoate, ran faster in response to the psychic drive of hunger. This dose of caffeine sodium benzoate is of the same order of magnitude as the doses used by us, which also resulted in a marked increase in coördinated activity. Similar effects have been described by others for coramine, and are well summarized

2 Eddy, N. V., and Downs, A. W., *J. Pharm. Exp. Therap.*, 1928, **33**, 167.

3 Cheney, R. H., *J. Pharm. Exp. Therap.*, 1935, **53**, 304.

4 Horst, K., and Jenkins, W. L., *J. Pharm. Exp. Therap.*, 1935, **53**, 385.

10 Skinner, B. F., and Heron, W. T., *Psychol. Record*, 1937, **1**, 340.

5 Miller, N. E., and Miles, W. R., *J. Comp. Psychol.*, 1935, **20**, 397.

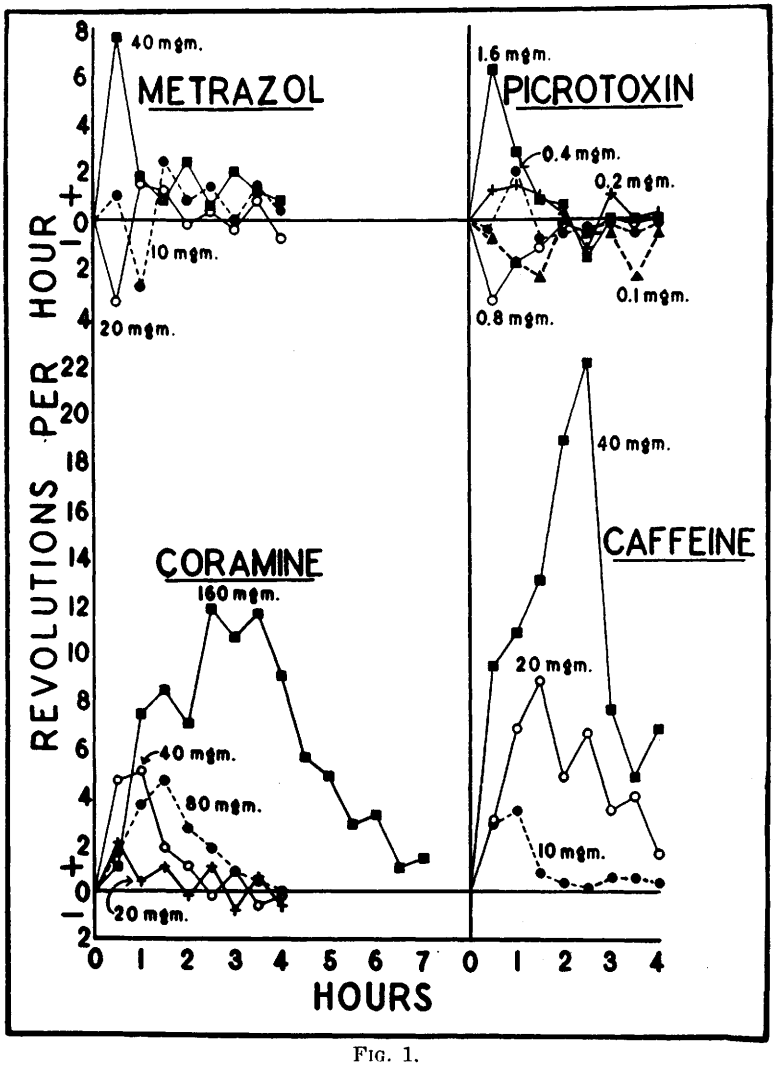

FIG. 1.

Stimulation of spontaneous muscular activity through the central nervous system in white rats produced by metrazol, picrotoxin, coramine and caffeine sodiobenzoate.

Each curve represents average net activity of 10 rats injected subcutaneously with the dose of the analeptic indicated, expressed in mg per kilogram.

by Hildebrandt.[6] For instance, according to Uhlmann, rabbits given this drug become excited, jump around, and show spontaneous activity of various types. Apparently, all parts of the brain, as well as the spinal cord, are almost equally sensitive to it. This phase of

[6] Hildebrandt, F., *Heffter's Handbuch der Experimentellen Pharmakologie*, 1937, **5**, 128.

cerebral stimulation has not been generally emphasized, inasmuch as the majority of workers have been interested primarily in the effects of these analeptics on respiration, circulation, or the recovery of consciousness. While the actions of picrotoxin are predominantly localized in the medulla, the stimulant action can extend below this area. Our results do not reveal supramedullary stimulation by subconvulsant doses, at least not of the kind which gives rise to spontaneous and coördinated muscular movements.

Metrazol was investigated by Jackson[7] from this viewpoint with the general result that the stimulants were not equally effective against various depressants, and metrazol caused tremors and convulsions with very little specific stimulation of the cerebral cortex. According to Hildebrandt's summary[8] its main effect consists in excitation of the central nervous system, with convulsions after large doses. However, it is not clear whether the drug affects the cerebral cortex or the psychic areas, rather than more caudal zones. Hildebrandt quotes Schoen, who attempted to localize the seat of action of metrazol by removing the cerebrum above the thalamus, but did not produce any alteration in metrazol-activity. This indicated that a considerable part of the metrazol stimulation was not derived from the higher levels of the nervous system. Winniwarter is quoted by Hildebrandt to the effect that typical convulsions are produced by metrazol in the decerebrate rabbit, thus indicating that metrazol attacks mainly the sub-cortical centers. Our results with metrazol are in agreement with those of previous workers, inasmuch as we failed to demonstrate any cortical type of stimulation, according to the criteria used.

Taking our results as a whole, it appears that metrazol and picrotoxin in doses below the convulsive level, do not produce increased motor activity, whereas coramine, caffeine, and cocaine cause increased activity of a coördinated voluntary purposeful type, and of an intensity proportionate to the dosage. Generalized convulsions are produced by those latter drugs only as the expression of an overwhelming degree of stimulation. Accordingly, the method used by us permits the differentiation of these two types of central stimulation in a rather clear manner, and is believed to be applicable in studies of other central stimulants. The method is also applicable to drug addiction studies as a means of obtaining record of changes in activity during habituation and withdrawal.

Summary and Conclusions. 1. A method is described for meas-

[7] Jackson, D. E., *J. Lab. Clin. Med.*, 1934, **20**, 1.

[8] Hildebrandt, F., *Heffter's Handbuch der Experimentellen Pharmakologie*, 1937, **5**, 151.

uring stimulation produced by analeptics, which consists of suspending white rats or other small animals in small cages from wire springs and summating the amount of movement by connecting the springs to Harvard work adders. The activities resulting over periods of hours, are recorded by electrical contacts on the work adders through signal magnets writing on a kymograph drum. The apparatus is kept in a lighted constant temperature chamber between 27 and 29°C as conditions for minimum activity. The amounts of activity shown by the animals after injections of normal saline solution are designated as control levels of activity, and subtracted from those observed during the action of a drug to give the net stimulation produced by the agent in question.

2. Metrazol, in doses from 10 to 40 mg per kilo, produced no increase in general activity except during convulsions resulting from doses of 40 mg. Picrotoxin, in doses from 0.1 to 1.6 mg per kilo also produced no increase in activity, except after doses of 1.6 mg, when the animals were in generalized convulsions. Therefore, these two agents showed no evidence of stimulating the higher levels of the nervous system, particularly the areas for purposeful coördinated movement.

3. Coramine, in doses of 20 mg per kilo, produced just perceptible degrees of increase of coördinated and purposeful activity, and with 40, 80, and 160 mg doses these changes were so large as to be unmistakable. The highest dose caused generalized convulsions in some animals. The actions of 160 mg persisted for about 7 hours, whereas those of 40 and 80 mg lasted 2½ and 4 hours, respectively.

4. Caffeine sodiobenzoate in doses of 10 mg per kilo, produced threshold increases in activity similar to that of coramine. Twenty mg per kilo caused larger increases and 40 mg produced very marked stimulation. The highest dose killed one of the 10 animals, so that higher dosage levels were not tested.

5. Cocaine in doses of 50 and 60 mg per kilo caused very marked stimulation resembling that of the highest doses of coramine and caffeine. The larger dose resulted in the death of one of the six animals used for this drug.

6. The margin of safety between the barely effective and convulsive or fatal doses of coramine was 8 times, and for caffeine, 4 times, indicating a narrower range for the latter drug under these conditions.

7. Therefore coramine, caffeine and cocaine stimulate activity in rats in a manner distinctive from that of picrotoxin and metrazol. The method differentiates between two kinds of central nervous system stimulation, and is suitable for study of the analeptic potency of

other agents, and for studies requiring measurement of spontaneous activity, such as in drug addiction.

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A Gas Machine for the Anesthetization of Small Laboratory Animals.*

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In connection with a problem dealing with the effects of various anesthetic gases on small laboratory animals (rabbits), it was necessary in the interest of safety and economy to construct an apparatus which could be attached to any standard clinical gas machine. After considerable difficulty, an apparatus meeting these requirements was designed. This apparatus makes it possible to supply anesthetic gases to the animal in rather constant concentrations.

The apparatus (Fig. 1) consists of a small soda-lime cannister and 2 flutter valves, mounted on a base 8 by 6 inches. Accurate quantities of the gases are measured by a large gas machine and are delivered into the small machine through the inlet tubing (A). The gases then pass over the flutter valve (B) and are delivered into the face mask. The exhaled gases pass through the flutter valve (F) and then through a small soda-lime cannister into the rebreathing bag. On inspiration, the mixture of gases from the rebreathing bag passes through the inspiratory flutter valve (B) to the animal. The small chamber above this flutter valve acts as a mixing chamber for the fresh and the rebreathed gases.

This constitutes a closed carbon dioxide absorption circuit and allows rebreathing of the anesthetic gases. The flutter valves (B and F) alternately open and close on inhalation and exhalation, thus compelling all gases to pass in one direction only. The rebreathing bag is a small rubber bag of 400 cc capacity. The metal bell-shaped face mask is covered with a rubber diaphragm in the center of which is a small opening to admit the nose of the animal. The tubing has an inside diameter of 8 mm. This apparatus permits small animals to be anesthetized with a minimal amount of anesthetic gases. The resistance of the gases passing through the machine is less than 2 cm