

seems to be concerned in some way with the dementias and psychoses and is probably the particular cell group which is concerned with the mental deterioration common to epilepsy. This nucleus is also concerned with the epileptic fit; especially such symptoms as dilation of the pupil, frothing at the mouth, cardiovascular disturbances and perhaps loss of consciousness through a disturbance of the cerebral blood supply. The nucleus *mammillo-infundibularis* and *nucleus tuberis* are probably secretory centers for the thyroid and parathyroid and are concerned with the muscular spasms characteristic of the epileptic fit and perhaps also in body temperature. There is as yet no indication as to which of these nuclei is a center for the thyroid and which for the parathyroid. It is likewise impossible to say what specific part each gland plays in the symptomatology. The epileptic fit is probably the result of a hyperactivity of the 3 nuclei of the infundibular region due to some strongly irritative agent to which some of the cells gradually succumb.

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Some Aspects of the Pharmacology of Apomorphine Hydrochloride.

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In spite of many chemical and pharmacological studies of apomorphine during the past 50 years, there still seems to be considerable doubt as to whether or not the green coloration which appears in apomorphine solutions is evidence of deterioration or of the formation of a new toxic substance. Guinard,¹ Eggleston and Hatcher² found little change pharmacologically in solutions of apomorphine which had become a deep green. Heinekamp,³ however, believed that such apomorphine solutions were definitely less potent. The United States Pharmacopoeia X, and some text books (*e. g.*, Trendelenburg⁴) recommend that solutions should not be used, especially if green immediately or shortly after the dissolving of the solid drug. Harnack⁵ declared that the oxidation with sub-

¹ Guinard, L., cited by R. Magnus, *Handb. d. exper. Pharm.*, II, pt. 1, 440.

² Eggleston, C., and Hatcher, R. A., *J. Phar. Exp. Ther.*, 1911-1912, iii, 551.

³ Heinekamp, W. J. R., *J. Lab. Clin. Med.*, 1922, viii, 165.

⁴ Trendelenburg, P., *Grundl. d. allg. u. spez. Arzneiverordnung*, Leipzig, 1926.

⁵ Harnack, E., *Arch. exp. Path. Pharm.*, 1874, ii, 254.

sequent loss of potency occurred with some apomorphine preparations and not with others. The experiments reported below were, therefore, in part, undertaken to determine the effect of oxidation of the dissolved drug (as shown by the green color of the solution) upon its pharmacological characteristics.

Three different crystalline preparations* of apomorphine hydrochloride were used for making both the new and the old solutions which were injected into 7 healthy unanesthetized dogs of from 7 to 11 kilos for 1 to 4½ months. Four of the 7 animals were injected daily for at least 4 months. The procedure finally adopted was to inject the animals once daily. Fresh solutions and green aged solutions of a given sample of apomorphine were administered on alternate days, subcutaneously. The minimal effective dose of 0.15 to 0.20 mg. per kilo was found to be the same as that reported by Eggleston and Hatcher. The data in Table I are representative of the results with injections over a period of 3 or 4 months.

TABLE I.
Potency of Fresh and Old Solutions of the Same Apomorphine Hydrochloride.

| Date | Animal | Apomorphine solution | Dose per kg. | Vomiting movements | | Remarks |
|---------------|--------|----------------------|--------------|-------------------------------|-----|--|
| | | | | First | No. | |
| Aug. 21, 1927 | 6 | Fresh | 0.15 mg. | Minutes after injection | 1 | Animals injected daily since May 18, 1927. |
| | 7 | " | " " | 9.5 | 1 | |
| Aug. 22, 1927 | 6 | 127 days old | " " | 9.2 | 1 | Solution black-green |
| | 7 | " " " | " " | 8.7 | 1 | |
| Aug. 23, 1927 | 6 | Fresh | " " | 8.6 | 1 | |
| | 7 | " | " " | 0.0 | 0 | |
| Aug. 24, 1927 | 6 | 129 days old | " " | 7.2 | 1 | Solution black-green |
| | 7 | " " " | " " | 8.7 | 2 | |

In green-black solutions at least 4½ months old and in one 12 months old, we found no pharmacological evidence of either quantitative or qualitative changes in the drug. The minimal effective dose was the same for the fresh solutions as for the old; the colored solutions caused no new or toxic effects. Injections made once daily into the dogs for 4 months produced neither hypersusceptibility (Richet⁶) nor tolerance to the drug.

Our experiments also indicated that, judged grossly, animals re-

* Made by Kahlbaum, Merck and Schuehardt.

⁶ Richet, C., *C. R. Soc. Biol.*, 1905, lviii, 955.

ceiving a "nauseant" dose of apomorphine daily for 4 months exhibited no pre-injection salivation similar to that observed by Tatum and Collins⁷ after 7 or 8 daily injections of morphine. Podkopaëff⁸ has reported the establishment of a conditioned salivary reflex in dogs by numerous injections of apomorphine hydrochloride accompanied by the note of an organ pipe. It therefore seemed necessary to determine as definitely as possible whether or not apomorphine did resemble morphine in establishing a conditioned salivary reflex. Accordingly, fistulae of Warton's ducts were made in 2 dogs to permit of a more accurate measurement of the salivary secretion as was done by Kleitman and Crisler.⁹ As before, however, the daily injection of apomorphine hydrochloride over an additional 3 months in a dose sufficient to provoke definite salivation, retching and vomiting never caused the appearance of a salivary conditioned reflex similar to that encountered after morphine injections. The data in Table II are typical and illustrate how the results were obtained.

TABLE II.
Salivary Secretion after Morphine and Apomorphine Injected Subcutaneously.

| Date | Animal | Secretion of saliva | | Remarks |
|---------------------------|--------|-----------------------------|----------------------------|--|
| | | 10 minutes before injection | 10 minutes after injection | |
| Dec. 11, 1927 | 6 | 6.0 cc. | 8.0 cc. | 30 mg. morphine hydrochloride given subcutaneously to each dog daily for 13 days previously. Daily injections of 0.2 mg. per kilo of apomorphine hydrochloride only, begun 18 days after last morphine hydrochloride injection. Apomorphine hydrochloride injections continued daily. Last apomorphine hydrochloride injection. |
| | 7 | 4.0 cc. | 7.0 cc. | |
| Jan. 8, 1928 1st day | 6 | 0.0 cc. | 7.0 cc. | |
| | 7 | 0.0 cc. | 10.0 cc. | |
| Feb. 15, 1928 39th day | 6 | 0.0 cc. | 3.8 cc. | |
| | 7 | 0.0 cc. | 3.2 cc. | |
| April 8, 1928 92nd day | 6 | 0.0 cc. | 2.0 cc. | |
| | 7 | 0.0 cc. | 1.9 cc. | |

The experiments of Henderson¹⁰ and others indicate that apomorphine has no peripheral action but stimulates the salivary centers and, unlike morphine,¹¹ does so even when injected into animals under anesthesia. Apparently apomorphine induces salivation, not so much by producing a nausea centrally, as by stimulating the motor cells of the salivary nuclei. This is in agreement with the

⁷ Collins, K., and Tatum, A. L., *Am. J. Physiol.*, 1925, lxxiv, 14.

⁸ Podkopaëff, N., cited in *Centralbl. ges. Neurol.*, 1925, xxxix, 214.

⁹ Kleitman, N., and Crisler, G., *Am. J. Physiol.*, 1927, lxxix, 571.

¹⁰ Henderson, V. E., *J. Phar. Exp. Ther.*, 1910, ii, 1.

¹¹ Kleitman, N., Personal communication.

frequently expressed belief that apomorphine may cause vomiting with little nausea. In our animals, dogs given apomorphine soon after eating a meal, commonly eat the vomitus immediately. This would hardly be possible if the animals were truly nauseated.

Summary: 1. The development of a green color in old (1 week to 1 year) apomorphine hydrochloride solutions appears to be accompanied by no qualitative or quantitative changes in the pharmacological actions of the drug.

2. Dogs receiving an emetic dose of apomorphine daily for 4 months exhibit no tolerance or hypersusceptibility. *No nauseant conditioned salivary reflex similar to that of morphine appears.*

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Chloride and Water Excretion After Intraperitoneal Administration of Salt Solution.

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Since Blackfan and Maxcy¹ pointed out the advantages of administering saline solution intraperitoneally in dehydrated infants, the method has been widely adopted, and is regarded as a most valuable therapeutic measure. If isotonic or slightly hypotonic solutions of saccharose are injected intraperitoneally in rabbits, in amounts of 100 ccm., a considerable diuresis ensues,² with an increased excretion of sugar. As a consequence we were interested in determining the output of water and chloride in acute experiments after similar injections of isotonic saline solution.

Male rabbits weighing between 2 and 2.5 kilos were used throughout the experiments, and were prepared according to methods previously outlined. Food was uniformly given as 200 gm. of carrots, 18 hours previous to each experiment. No additional water was given. A large soft rubber catheter a demeure was used to collect the urinary output. Specimens were collected during 10 minute periods for one hour or more, and at the middle of each 10 minute period 0.2 ccm. of blood was drawn from an ear vein

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¹ Blackfan and Maxcy, *Am. J. Dis. Child.*, 1918, xv, 19.

² Curtis, *Biochem. Z.*, 1925, elxiii, 109.