or combined with fatal dose) method whose value and applications have been sufficiently established.

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A STUDY OF THE TOXICITY AND ANTIPYRETIC ACTION OF D. GLUCONO-PARA-PHENETIDIN.*

BY HERBERT A. BRAUN AND GEORGE F. CARTLAND.[1]

Within the last decade a number of synthetic modifications of acetphenetidin and acetanilide have been studied in an attempt to increase the antipyretic and analgesic action of these compounds or to reduce their toxicity.

Hambourger[2] has reported pharmacological studies on the gluconic acid derivative of para-phenetidin $C_6H_{11}O_6NHC_6H_4OC_2H_5$. He finds that this compound has a very low toxicity as compared to acetphenetidin when administered orally to rats. He states that, as an antipyretic, it is about as effective as acetphenetidin when administered in equimolecular portions to rabbits which had been fevered with hay infusion.

We have completed a study of glucono-para-phenetidin in which we have confirmed the findings of Hambourger regarding the relatively low toxicity of this compound as compared to acetphenetidin. However, in contrast to Hambourger's report, we found that glucono-phenetidin exerts a much lower antipyretic action in fevered rabbits than that produced by equimolecular quantities of acetphenetidin.

ACUTE TOXICITY.

Glucono-phenetidin was administered as a suspension in 5% acacia to albino rats by means of a stomach tube. Since the quantity of this drug was too great to be administered in one dose, three divided doses were given over a period of three

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hours. The minimum lethal dose (M. L. D.), or the dose which killed more than 50% of the rats, was found to be greater than 50 Gm. per Kg. of rat.

Parallel experiments were conducted to determine the acute toxicity of acetphenetidin. The results given in the table indicate that the M. L. D. for this drug is 2 Gm. per Kg. of rat. The maximum tolerated dose (M. T. D.), or the dose at which toxic symptoms appear, was found to be 0.75 Gm. per Kg. Toxic symptoms observed were cyanosis, slow respiration, depression, loss of equilibrium, coma and finally death.

TABLE I.—COMPARATIVE TOXICITY OF GLUCONO-PHENETIDINE AND ACETPHENETIDIN.

Glucono-phenetidin.			Acetphenetidin.		
Dose per Kg./Gm.	No. of Animals Used.	% Mortality.	Dose per Kg./Gm.	No. of Animals Used.	% Mortality.
20	5	0.0	0.75	2	0.0
30	5	0.0	1	4	0.0
50	5	0.0	2	10	60
			3	10	90
			4	5	100
			5	2	100

By means of spectroscopic examination of the blood of depressed rats, methemoglobin formation could be detected when doses of 1 Gm. per Kg. of acetphenetidin were administered. At no dose of glucono-phenetidin could the presence of appreciable amounts of methemoglobin be determined, indicating that it is quite resistant to destruction in the intestinal tract which accounts for the greatly decreased therapeutic activity of the substance.

ANTIPYRETIC ACTION.

Rabbits were used as experimental animals. They were starved for forty-eight hours and were given no water for twenty-four hours. At the end of this time, the animals were fevered by injecting 10% hay infusion which had been incubated at 37° C. for twenty-four hours. Five cubic centimeters of this infusion per Kg. of rabbit were injected subcutaneously. Normal rectal temperatures were taken at the beginning of the experiment. Two hours were allowed to elapse after the injection of the hay infusion before a second reading was taken. Increases in temperature varying from 0.5°–2° C. over the normal were attained. When the fever temperature was reached at the end of the two hours, the drugs suspended in a 1% acacia solution were administered to the rabbits by means of a stomach tube. Rectal temperatures were taken at hourly intervals during the course of the experiment.

In the majority of the experiments, ten rabbits were used for each trial. From one to three trials were attempted for each dose. Of the ten rabbits used two served as room temperature controls, two as fever controls, three were given acetphenetidin and three glucono-phenetidin. Six doses of the drug were administered. The doses of the first three trials were calculated on the basis of molecular weight, the ratio of glucono-phenetidin to acetphenetidin being 7:4. In the last three trials, 0.75 Gm. per Kg., the dose which was found to give an optimum depression of the temperature for acetphenetidin was compared with multiples of the equimolecular dosage (1.31 Gm.) of glucono-phenetidin.

(1) 0.50 Gm./Kg.	of acetphenetidin	to 0.87	Gm./Kg.	of glucono-phenetidin.
(2) 0.60 "	"	1.05	"	"
(3) 0.75 "	"	1.31	"	"
(4) 0.75 "	"	2.62	"	"
(5) 0.75 "	"	5.24	"	"
(6) 0.75 "	"	10.50	"	"

In the first three trials where molecular equivalents of glucono-phenetidin were compared with acetphenetidin administered at 0.50, 0.60 and 0.75 Gm. per Kg., the acetphenetidin was much superior to glucono-phenetidin in causing a depression of the temperature in fevered rabbits. The dosage of 0.75 Gm. of acetphenetidin per Kg. produced an optimum depression of temperature and consequently was chosen as a basis of comparison for higher doses of glucono-phenetidin which were 2, 4 and 8 times the equimolecular dosage. In each case, the antipyretic effect of glucono-phenetidin was less than that of acetphenetidin. In Chart I, the temperature curves of fevered rabbits treated with acetphenetidin 0.75 Gm./Kg. and glucono-phenetidin 10.5 Gm./Kg. are compared with the untreated controls. Each curve represents the average values obtained with five rabbits. Acetphenetidin caused a greater depression of temperature which lasted for more than five hours while the temperature of the fevered rabbits receiving glucono-phenetidin was above normal after two hours.

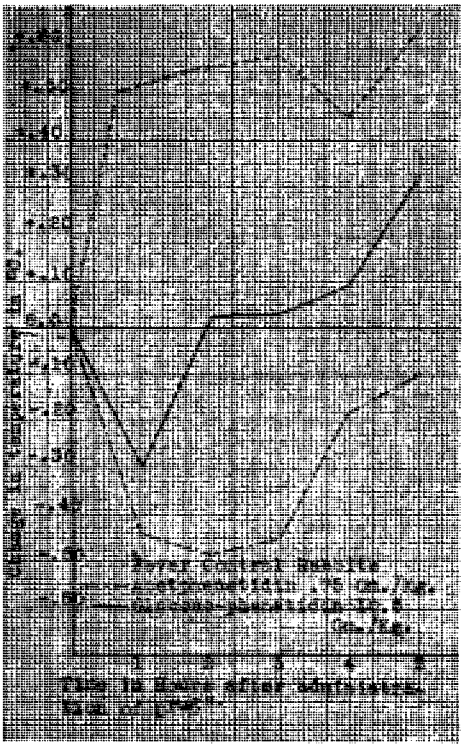

Chart I.

CONCLUSIONS.

(1) A study of the toxicity and antipyretic action of glucono-phenetidin and acetphenetidin has been completed and is described.

(2) Toxicity. Glucono-phenetidin was found to be non-toxic in doses of 50 Gm./Kg. in the rat confirming previous results. The M. L. D. of acetphenetidin was found to be 2 Gm./Kg. of rat which means that glucono-phenetidin is twenty-five times less toxic than acetphenetidin in the rat. The M. T. D. for acetphenetidin is 0.75 Gm./Kg. of rat.

Methemoglobin formation was not observed with glucono-phenetidin but was noted with 1 Gm./Kg. of acetphenetidin.

(3) Antipyretic Action. Acetphenetidin and glucono-phenetidin were not found to be approximately equal when administered on the basis of their molecular weights using the 4:7 ratio. When the dosage of glucono-phenetidin was increased

to eight times that required by this ratio, its antipyretic effect was still less than that produced by acetphenetidin.

The above findings conform with previous conceptions of investigators in the field of antipyretics, namely, that the toxicity and therapeutic activity of antipyretics decrease with an increase in the size of the substituted radical. The most effective compounds have the ethyl or acetyl grouping.

(*A Paper of Scientific Section—"A Chemical Study of the Fixed Oil of Poke Root"—Page 636.*)

DRUG STANDARDIZATION.*

BY E. R. SERLES.[1]

It is a far cry from our modern conception of rational therapy to the time when the medical code of Hammurabi prescribed that the suffering Babylonians should treat their ills by charm, employing precious stones, frankincense or, what was even worse, the oral administration of lizard's blood, swine's teeth, moisture from pigs' ears, excreta of human beings, animals and even flies.

Yet the toad skin which was used in those days without the slightest inkling of its real merit is to-day known to contain substances which act much like digitalis. Trendelenburg in 1909 isolated toxic principles from the skin of the common toad (Bufanin and Bufotalin) which produced the typical therapeutic effects of digitalis.

Ma Huang, the Chinese plant Ephedra, has been known in Chinese medicine for more than 3000 years, but it remained for Chen and his co-workers to show us its relationship to adrenalin and its superiority to the latter in certain instances.

Bones may not have been judiciously administered during the age of Ptolemy; lizard's blood would hardly be classed as appetizing; yet it is a significant fact that some of our great packing plants can afford to sacrifice the carcasses of their daily slaughter at extremely low figures because of the profits taken from the sale of glandular extracts and preparations made therefrom.

How glibly we jest about the food we eat, asking ourselves about the vitamins it should yield. We may or may not take much stock in the claims made that certain drugs and food products are essential to growth and health and thereby eliminate disease, yet the pharmacist who still urges his customer to try a bottle of some standard blood purifier or the physician who still prescribes strychnine as a heart stimulant is only a shade ahead of the pharmacist who prepared a prescription for Schesch (a queen of the third Egyptian dynasty) which contained equal parts of the heel of an Abyssinian greyhound, of date blossoms and of asses' hoofs boiled in oil, recommending the same for a hair restorer.

The early history of the practice of the "Healing Art" is filled with countless instances of confusion, quackery and jealousy. For hundreds of years suffering humanity was the victim of the charlatan, the knave and superstition.

Gradually the more learned men of science began to break down the severe censorship of church and state and the chaos of knowledge concerning diseases and their treatment took on a more rational aspect.

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