SOME FACTS CONCERNING THE PHARMACOLOGICAL AND PHYSIOLOGICAL ACTION OF ACETANILID.*

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The object of this paper is to present, without elaboration at this time, some facts obtained by animal and clinical experimental work concerning the action of acetanilid.

For years opinions concerning the action of this drug have obtained which pharmacological and clinical evidence prove to be erroneous.

Many errors in the literature appear to be there for the reason that no one has taken the trouble to disprove them, so they remain and grow and pass from year to year, from book to book.

The following topics are considered of sufficient importance to be included:

(1) The toxic dose when the drug is given by mouth.
(2) The minimum lethal dose.
(3) The effect of continuous ingestion.
(4) The effect upon the circulatory system.
(5) The effect of continuous use as determined by clinical experimental work.
(6) Occurrence of untoward effects as shown by hospital records.
(7) Acetanilid and cyanosis.

THE TOXIC DOSE.

In this investigation, all the usual laboratory animals have been used, and the doses were given in terms of milligrams per kilogram, so that each milligram corresponds to one grain for an average sized adult.

Briefly, the manifestations of toxic action become evident in the following order and character:

100 mg. per Kg. cause no evidence of toxic action.

200 mg. per Kg. cause dogs to salivate some, but cause no signs in other animals.

400 mg. per Kg. produce marked salivation in dogs, with restlessness. In rabbits, the toxic action is shown by weakness in the hind legs, but the animals move about and eat. Rats become moderately depressed but come to the cage door for food. All animals completely recover by the next day.

800 mg. per Kg. cause marked increase in all of the above signs, and in addition dogs and rats develop dyspnœa. All recover.

1000 mg. per Kg. have repeatedly failed to produce fatal results.

THE MINIMUM LETHAL DOSE.

The M. L. D. for guinea pigs and for rabbits is 1500 mg. per Kg.

For rats it is 2400 mg. per Kg. given by stomach tube in 50% alcohol.

Dogs have not been given more than 1000 mg. per Kg. due to the large amount of fluid required to wash the drug into the stomach. This much is not fatal to the dog.

Mice survive up to 1350 mg. per Kg. given hypodermically.

THE EFFECT OF CONTINUOUS INGESTION.

Mice.—Although the M. L. D. for mice, when injected hypodermically, is 1350 mg. per Kg., mice take half this amount daily in drinking water, with no

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effect upon them except a delay in growth, which is recovered from when the acetanilid is withdrawn.

These animals taking 500 mg. per Kg. per day for a month, triple their weight. They take 325 mg. per Kg. plus 60 mg. per Kg. of caffeine for a month, with no deleterious effect.

(Personal communication from Dr. H. A. McGuigan, University of Illinois, Department of Pharmacology. Extract of this work appeared in the July issue of the *Journal of Pharmacology and Experimental Therapeutics*.)

Rats.—Rats given 5 to 10 mg. per Kg. per day in milk, through four generations, reproduce in normal numbers, develop normally, care for their young and show no deviation in morbidity or mortality from the average for an unmedicated rat population.

Rats given 250 mg. per Kg. in 50% alcohol daily for two weeks, show no anemia in daily blood pictures and examination of the bone narrow at the end of this time shows it to be normal.

Rabbits.—Rabbits given 10 mg. per Kg. twice daily for 3 months, and the same amount four times daily for a second 3 months, gain 200–400 Gm. and monthly examinations of blood and urine disclose no pathological findings in either.

Dogs.—Two dogs carried for three months on four grains twice daily, have grown normally, and maintained normal appetites and good general condition. One had pups, and received the drug through gestation and lactation. All pups lived and reached maturity.

Two dogs receiving five grains each, twice daily, for a year, progressed normally, the blood and urine remained normal, as shown by monthly examinations, and no spectroscopic changes developed in the blood.

Autopsy of the animals at the end of this period, with histological examination of cardiac muscle, liver, spleen, kidneys, brain and cord, has shown no pathological changes.

THE EFFECT UPON THE CIRCULATORY SYSTEM.

When acetanilid, in fatal amounts, is injected intravenously, animals do not die a cardiac death, but a respiratory death.

A large number of myocardiographic tracings have been made upon dogs under Nembutal anesthesia that bear this out.

A dog was given two grains by stomach tube every half hour for 12 doses, and another was given four, and another 12 at like intervals, and no changes were produced in the tracing.

One-drachm doses were given by mouth, with no significant changes occurring.

One drachm introduced directly into an intestinal loop, through an enterostomy, caused no depression of the circulation, when observed over a whole day.

Although conclusions should not be drawn from intravenous injections, this was also done. 100 mg. per Kg. as a 0.5% solution in sodium chloride was infused, at hourly intervals for a whole working day, with no evidence of depression.

Alcohol—20 cc. of 35% solution—intravenously, produced depression quickly recovered from. Repetition of this dose twice was fatal.

Ten cc. of mucilage acacia intravenously produced a change in the tracing,

identical with that caused by 10 cc. of the same solution to which had been added 5% acetanilid.

THE EFFECT OF CONTINUOUS USE AS DETERMINED BY CLINICAL EXPERIMENTAL WORK.

Ten individuals were given 4 grains of acetanilid at 9:00–9:30 and 10:00 A.M. daily, for a period of 16 weeks and were subjected to weekly examinations with the following findings:

(1) No changes in physical examination as shown by weekly check ups.

(2) No effect on nervous system as evidenced by expert neurological examination.

(3) No effect on heart muscle or conducting mechanism as evidenced by weekly electrocardiograms, by well-sustained blood pressure, and physical examination of the heart.

(4) No effect on metabolism as shown by B. M. R.

(5) No methemoglobin formation or other spectroscopic changes as shown by spectroscopic examination of the blood.

(6) No effect on kidneys as shown by kidney function, tests and urinalyses.

(7) No changes in blood chemistry findings.

(8) No blood destruction as evidenced by the fragility, the Van den Bergh test and icteric index.

(9) A transitory effect upon hemopœsis as shown by initial slight changes in red cell counts which soon return to normal and are found normal at the conclusion of the test.

OCCURRENCE OF UNTOWARD EFFECTS AS SHOWN BY HOSPITAL RECORDS.

Statistical data were secured by mailing questionnaires to all of the hospitals and institutions in the United States. Replies were received, which represented 2,500,000 hospital admissions annually for 10 years, or a total of 25,000,000 people.

Total poisonings in the records of these institutions were 5.6 per million and deaths 0.16 per million.

Similar figures concerning the barbituric acid derivatives for poisonings were ten times that of acetanilid and for deaths were nine times as large.

The significance of these figures is in the way these drugs are used. The frequency of the use of acetanilid, in various preparations, far exceeds that of the hypnotic group. The acetanilid group is used largely by the laity for self medication, while the use of the hypnotic group is to a larger extent in the hands of physicians.

In this connection an interesting observation is made in the Prescription Ingredient Survey. The use, by prescription of acetanilid and phenacetin has decreased, the former markedly, the latter less so, while the use of the hypnotic compounds has increased to such extent that they occur more than once in every ten prescriptions or about 28,700,000 times a year.

ACETANILID AND CYANOSIS.

It is now apparent that the cyanosis seen in rare instances in connection with the alleged use of acetanilid is not dependent upon the use of drugs. The condition is always associated with constipation, and is only relieved when the constipation is relieved. The cause lies in an abnormality within the individual himself. A study of the fifty cases of this condition reported in the literature discloses that the taking of drugs was ruled out in thirty-six.

The abnormal hemoglobin derivative developed is not methemoglobin but is sulphurhemoglobin. This compound is formed by the action of hydrogen sulphide on the blood, and as acetanilid contains no sulphur it cannot be the cause of the condition.

CONCLUSIONS.

1. The toxic dose of acetanilid is about 100 times the therapeutic dose.
2. The M. L. D. in general agrees for all laboratory animals and is around 1500 mg. per Kg. or 500 times the therapeutic dose.
3. Continuous ingestion of large amounts has no deleterious effects upon animals.
4. Acetanilid is not a circulatory depressant.
5. Twelve grains a day for 16 weeks has no deleterious effect upon human subjects.
6. In the hospital records of the United States, cases of poisoning and deaths from the drug are of insignificant number.
7. In the hands of the Medical Profession, the use of these analgesic drugs has largely been replaced by the use of intellectually depressant, or sleep-producing, drugs.
8. The cyanosis seen at times in connection with the use of these drugs is not dependent upon drug action, but upon an individual predisposition of the user.

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THE CHEMICAL AND PHARMACOLOGICAL PROPERTIES OF CALCIUM ACETYLSALICYLATE.*[1]

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During the past year, we have had an opportunity to examine several powder and tablet preparations of calcium acetylsalicylate. Inasmuch as this substance is marketed abroad while little information concerning it is available in American literature, we thought it worth while to record our observations with respect to its chemical, physical and pharmacological properties.

The following preparations were available for testing:

1. Kalmopyrin. Tablets and powder of calcium acetylsalicylate manufactured by the Chemical Works of Gideon Richter, Budapest.
2. Calcium Acetylsalicylate. Tablets and powder made for us by Arner and Company, Buffalo, New York.
3. Calcium Acetylsalicylate. Powder prepared in the laboratory.

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[1] Scientific Section, A. PH. A., Madison meeting, 1933.