In general, the lower the concentration of these chemical substances, the better was the growth response. Concentrations of 0.025% or greater were found to produce the most toxic effects.

Pyridine, piperidine and atropine sulfate induced marked inhibitory stem growth responses during a period of sixty-day treatments. However, leaf growth was not appreciably impaired during the same period. A condition of roughened leaves has been described for some seedlings treated with piperidine and atropine sulfate. This response was found to be similar to that previously reported for stramonium seedlings treated with colchicine (1).

Epinastic responses and other toxic manifestations varied according to the size and the rate of growth of the seedlings.

Thiamin chloride accelerated growth responses. Concentrations of 0.001% and 0.0025% produced the most vigorous growth activity.

The fact that stramonium plants are influenced to some extent in stem and leaf growth by those substances which have a chemical structure related to the atropine nucleus and that they can tolerate small concentrations of these chemicals indicates the possibility that by feeding the plant continuous tolerated doses, the alkaloid content in the leaves might also be influenced. This phase of the experiment is being continued and will be reported subsequently.

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A Note on the Healing Action of Allantoin, Allantoin Dipiperazine and Urea*

Preliminary Report

By Frederick R. Greenbaum

The reintroduction of allantoin clinically occurred in 1935 through the work of Robinson (1) who demonstrated that one of the active principles of the excretion of maggots is allantoin. Greenbaum (2) reported on the healing action of allantoin in various clinical cases. In another publication by Robinson (3) it was shown that urea is present in the extracts of maggots, and that it also possesses healing action. Since this publication appeared, several investigators have tried urea to stimulate healing in chronic purulent wounds and in infected wounds (4, 5, 6, 7).

Urea is inexpensive, and therefore some clinicians might prefer to use urea provided it is as effective as allantoin. Holder and Mackey (7) used a 40% urea solution and also crystals of urea. Forty per cent urea solution has a tendency to dry and cake on occasion, and there is difficulty in maintaining it in proper contact with the tissue at times. The use of concentrated urea solution is frequently accompanied with pain so pronounced that it is necessary that a local anesthetic be added to the concentrated urea solution.

EXPERIMENTAL

The purpose of this investigation was to demonstrate by means of animal experiments the relative healing properties of allantoin and urea. We also included in this investigation a combination of allantoin with piperazine, which is more soluble than allantoin. This combination is a double salt of allantoin with piperazine. It was prepared by dissolving 2 moles of piperazine in water and 1 mole of allantoin. The maximum solubility of

* This work was carried out at the Research Laboratories of the National Drug Company, Philadelphia, Pa.

Table I

Animal	Weight	Nature of Burn	Time of Healing in Days of Burns Treated with—Allantoin	Saline Solution	Allantoin Dipiperazine	40% Urea	Remarks
Rabbits, 2	2 Kg.	Hot soldering iron	13	13	13	..	Granulation occurred after 5 days
Rabbits, 2	2 Kg.	Hot soldering iron	14	14	14	..	In 2 days showed signs of repair
Rabbits, 2	2 Kg.	Sodium hydroxide	8[a]	..	..	..	Rabbits died
Rabbits, 4	2 Kg.	Sodium hydroxide	25	25	27	30	
Pigeons, 2	...	Sodium hydroxide	14	21	..	..	
Roosters, 4	3 Lb.	Sodium hydroxide	14	19	20	27	

[a] Evidence of healing.

allantoin at room temperature is 0.6%. Piperazine increases the solubility so that 6% of allantoin remains in solution at room temperature.

Our attention was directed to a paper by Milles and Farley (8) who studied a comparison of the effects of an antiseptic jelly, with and without larvæ ingredients, on burns produced with a red-hot iron. These workers showed on a group of rabbits the superiority of healing obtained with a jelly containing comminuted larvæ *Lucilia sericata* over a plain jelly without the larvæ material.

The study here reported is our observation concerning the comparative healing action of allantoin and allantoin dipiperazine on experimental animals.

Table I gives a short account of the healing action of allantoin, saline solution, allantoin dipiperazine and 40% urea. The time given indicates when complete healing occurred.

DISCUSSION OF RESULTS

It was demonstrated on a very limited number of animals in a very preliminary way that the healing action of allantoin is superior to that of allantoin dipiperazine. However, under our experimental conditions, rabbits are not entirely suitable for this type of experiment due to the fact that they are fur-bearing animals.

Using pigeons, the definite healing action of allantoin solution and of allantoin ointment was again demonstrated, but pigeons are rather small for this test.

We therefore selected roosters and found them more suitable for this study. It was in the roosters that we demonstrated that allantoin has the best and quickest healing action, completely healing a chemical burn in a rooster in 14 days. In the control bird that was treated with saline solution, the healing required 19 days; with allantoin dipiperazine, 20 days; and with 40% urea solution, 27 days. These experiments clearly show that 40% urea solution greatly retards the healing. It also shows that the allantoin dipiperazine is inferior to the plain allantoin. The explanation of this behavior is, however, in complete agreement with the chemical nature of this compound of allantoin. It has been found that an allantoin dipiperazine solution has a greater solubility than allantoin and the solution thus obtained is very alkaline in nature (*p*H 11 or more). Therefore, as the high *p*H destroys the allantoin, allantoin dipiperazine is decomposed in solution and most of the allantoin is chemically broken down, and therefore loses its healing potency.

The healing action of allantoin is based on the stimulation of epithelial growth, while the healing action of urea is based on the removal of devitalized tissue.

Macalister (9) offers the theory that allantoin may possibly have something to do with the activity of nucleic acid. In the chemical makeup of nucleic acid, we have a phosphoric acid residue linked to a pentose sugar and to adenine, thymine, guanine, or cytosine. These latter substances are purine bodies, and it is to these purine bodies that allantoin may be indirectly related since purine bodies yield uric acid in the course of their chemical metabolism, while uric acid when suitably oxidized yields allantoin.

It seems reasonable to suppose that cellular stability may depend upon the efficient building up of nucleic acid. The connection between nucleic acid and allantoin is, however, a very indirect one. This is only a hypothesis; no definite proof has been furnished.

There is some evidence, as reported by Greenbaum (10), that the administration of allantoin produces leucocytosis in animals. This opens up the possibility that allantoin exerts its healing action partly through a local leucocytosis which sets in at the site of the wound.

Much more research with a greater number of animals is necessary before any definite conclusions may be drawn.

SUMMARY

1. Rabbits are fur-bearing animals, and, therefore, are not satisfactory animals, under our experimental conditions, to test comparatively the healing action of various proliferative substances.

2. Pigeons, on the other hand, are birds

which are too small to be profitably used for this type of experimentation.

3. Roosters appear to be suitable for this type of study.

4. While the number of animals is undoubtedly very limited, it has been shown that of the four agents studied—allantoin, allantoin dipiperazine, 40% urea and physiologic salt solution—allantoin possesses the best healing action, urea the least.

5. Allantoin dipiperazine shows no better healing or granulating action than saline solution because the alkalinity of the solution destroys the allantoin, and thus the potency.

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A Study of Syrup of Hydriodic Acid*

By Howard Hopkins† and C. O. Lee‡

The solution of hydriodic acid from which the syrup was first prepared was unstable due to the presence of potassium iodate in the potassium iodide. Discoloration of the syrup in years gone by may have been due to the liberation of free iodine. With the coming of more highly purified chemicals its discoloration has been ascribed to other causes. Since about 1880 there have been numerous comments and discussions by many workers on how best to prepare, stabilize and store syrup of hydriodic acid.

Hydriodic acid has been used in medicine for more than a hundred years. Because of its unstable character it has been a problem. Many studies have been made with the view to finding a more suitable method for its preparation and preservation.

The first to report the use of hydriodic acid as a medicinal was Dr. Andrew Buchanan, Junior Surgeon to the Glasgow Royal Infirmary in 1837 (1, 2, 3). He gave detailed directions for the preparation of a dilute solution of the acid by the interaction of potassium iodide and tartaric acid. He preferred to use the acid, in the place of iodine, because he believed that it was less irritating to the stomach. He believed, also, that the stomach converted iodine into hydriodic acid, which reaction would be saved by administering the latter preparation. Buchanan proposed that the acid should be taken with starch gruel, arguing that any iodine which might be liberated would combine with the starch, and be less irritating.

Apparently the first attempt to stabilize the solution of hydriodic acid was reported in 1855 by Murdock (3). He said, "I find that hydriodic acid may be prevented from undergoing this decomposition when in the form of a syrup." He said further, "Assuming, therefore, that if a syrup can be prepared by Dr. Buchanan's solution that shall contain no free iodine, it will furnish the most suitable manner of obtaining this acid for medicinal purposes....It is necessary, however, to observe, as one of the conditions of success, that the iodide must be free from any trace of iodate of potash."

The U. S. Pharmacopœia IV (4) included a formula for diluted hydriodic acid, and

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