

poured into 1500 cc. of water. The sticky precipitate was washed free of acid with water and mercurated without further purification, because attempts to crystallize this substance led to decomposition with the formation of red coloring matters.

The hot solution of 23 Gm. mercuric acetate in 100 cc. of water and 5 cc. glacial acetic acid was added to a refluxing solution of 11 Gm. crude 3,3'-dibromo-4,4'-dihydroxydiphenyl-dimethylmethane with continuous stirring. About fifteen minutes were required for the addition of the mercuric acetate solution. A white precipitate commenced to form during the addition of the mercuric acetate and continued for about 45 minutes. At the end of this time inorganic mercury could no longer be detected in the solution. The latter was cooled and the heavy white precipitate collected by filtration, washed with ether and dried.

Yield, 18 Gm.

M. p.—decomposes 250° C.

0.1704 Gm. gave 0.0775 Gm. Hg.

Hg found, 44.5%.

Calculated for $C_{19}H_{18}O_6Br_2Hg_2$, 44.5%.

The product formed a white amorphous powder, insoluble in the common organic solvents but soluble in a considerable excess of alkali hydroxide solution.

The mercury analyses reported here were carried out by the Whitmore gold crucible method.

The biological tests on compounds reported herein were made in the Biological Research Laboratories of E. R. Squibb and Sons and we gratefully acknowledge their assistance.

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VEGETABLE EXTRACTS AND BLOOD-SUGAR.*

BY PAUL S. JORGENSEN AND E. V. LYNN.

Just after the discovery of insulin Collip (1) prepared from various vegetables, as well as from animal tissue, extracts which were capable of producing hypoglycemia in animals. The effects differed from those by insulin in requiring a comparatively long period before their appearance. A further very interesting observation he made was that the serum or defibrinated blood of an animal, made hypoglycemic by insulin, by the plant extracts, by chemicals, by starvation or by pancreatectomy, had similar marked lowering effect on the sugar in another animal and could even cause death. The decrease in sugar and toxicity could thus be transmitted from one individual to another, apparently without limit.

Thalkimer and Perry (2), in a very limited study, reported an insulin-like action by injection of raw potato juice. Winter and Smith (3) noted similar results from extracts of yeast. Others (4) have partly confirmed or directly contradicted this testimony.

In 1927 Allen (5) described the action of myrtomel (earlier called myrtillin), an extract made from leaves of the genus *Vaccinium* by a process similar to that for

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isolating insulin. It had no effect on the sugar in normal, fasting animals but reduced or completely suppressed the hyperglycemia following the administration of large quantities of dextrose to dogs and men and diminished the glycemia and glycosuria from epinephrine. The most striking characteristic was an apparent storage, since the effects lasted several weeks after a single dose of 1 Gm. Larger amounts did not increase this effect and were entirely non-toxic, as was also continual administration over long periods. Furthermore, the blood-sugar of totally depancreatized dogs was stabilized by ingestion of myrtomel and the span of life was increased four to five weeks.

Clinical experience, which was at that time much less striking, has not been particularly encouraging. Of 81 diabetic patients, Allen found that 36 were benefited and in 6 it was possible to stop the use of insulin entirely (18 to 54 units daily). More recently he came to the conclusion that there is no definite insulin-replacing effect. Myrtomel was afterward placed on the market for experimental purposes, but its subsequent withdrawal and abandonment would seem to indicate that others could not get satisfactory results in diabetes.

Others have attributed similar properties to extracts of various plants: grapefruit by Taylor and Atter (6), later refuted (7); fragrant sumac and bugleweed (8); alfalfa, clover, corn silk, etc. (9); species of *Vinca* (10). Poole, in an unpublished work here, found similar results from extracts of *Gaultheria shallon* (salal), of *Vaccinium ovalatum* and of *V. parvifolium*.

We started the present investigation to determine the nature of the substance responsible for this power to reduce the amount of sugar in the blood.

EXPERIMENTAL.

Rabbits, which were used as test animals, were kept on a standard diet, which was satisfactorily adequate, and under conditions as nearly ideal as possible. The withdrawal of blood for analysis was made at fixed times of day and under equal conditions otherwise.

After a large number of trials, it was found that the normal amount of sugar in the blood could be placed approximately at 0.109 ± 0.009 per cent, using the Shaffer-Hartmann method of determination (11). In a similar series of experiments it was found that 0.5 mg. of epinephrine gave about 0.176 per cent sugar in 90 minutes and 0.196 in 120 minutes, while 1 mg. of epinephrine gave 0.278 and 0.294 per cent, respectively, in the same times.

An extract was made from the leaves of salal by Allen's method and fed to rabbits in a dose of 1 Gm. daily (equivalent to 50 Gm. of leaves) for several days. No effect could be observed on the level of blood-sugar nor on epinephrine hyperglycemia which was produced every day during the experiment. Subcutaneous injections of the extract, equivalent to 60 Gm. of the leaves, were likewise without effect, as were also injections of fractions made by dialysis and of aqueous and alcoholic extracts of the leaves. In no case could active material be found.

Similar negative results were found with *Vaccinium ovalatum*. In no instance could any extract or fraction be found to alter the normal level of blood-sugar or that after action of epinephrine. We are convinced after hundreds of experiments that the solutions made in various ways have no power to reduce the amount of sugar.

In view of the circumstances it seemed advisable to repeat some of the work on myrtomel. Allen (5) described preparations from two species of *Vaccinium*, but the myrtomel later used by experimenters came from an unknown source and according to the manufacturers, the species used is immaterial. Consequently, a sample of leaves from *V. dumosum* was obtained from near Sudbury, Massachusetts, extracted and tested on rabbits. Again results were entirely negative, since orally or by injections no effect on blood-sugar, either normal or after epinephrine, could be obtained by amounts equal to 50 Gm. of leaves.

At this stage the problem began to take on a different light and we were forced to consider

it from the negative viewpoint. Possibly such preparations from plants do not have an effect on sugar metabolism, in spite of reports to the contrary. With this in mind, it was decided to repeat the earlier work of Collip (1).

An alcoholic extract was made from green onion tops and concentrated according to his method. This was injected daily as before in amount equal to 20 Gm. of original material. There was made also an aqueous extract from the onion tops and injected in the same amount. Although many such tests were performed, we could never note any change in the normal amount of sugar nor in the level after injection of epinephrine.

Exactly similar results were obtained with fresh lettuce leaves (25 Gm. daily) and with fresh cabbage leaves (20 Gm. daily). In all cases the methods of preparing the extracts were according to Collip.

In order to make the matter still more convincing, we tested some of these preparations on a depancreatized dog. The animal lived for more than five days, during which time there were injected at various periods extracts equivalent to 100 Gm. of huckleberry leaves, to 100 Gm. of salal leaves and to 60 Gm. of fresh lettuce leaves. In no case was the curve of blood-sugar altered. Insulin was capable of lowering the amount of sugar but could not prevent death in coma on the sixth day.

The interesting observation by Collip that hypoglycemia could be transmitted from one animal to another next engaged our attention. He found that, if a rabbit was rendered low in blood-sugar by insulin, by plant extracts, by guanidine derivatives or by starvation, injection of its serum or defibrinated blood would confer a similar condition on a second animal.

An attempt was made to confirm this for insulin. A rabbit, given 20 units of the latter by injection, was in a state of violent convulsions three hours later. While in this condition it was bled and the blood was defibrinated by whipping. A second rabbit was injected with 10 cc. of this product and then observed for more than a week. The amount of sugar in the blood was normal at all times and it exhibited no unusual symptoms. Several repetitions of this experiment gave the same result.

DISCUSSION.

From a study of the results herein contained and those of previous experimenters, we are forced to conclude that the reputed therapeutic value of plant extracts in the control of sugar is erroneous.

Collip's work may be criticized from the standpoint of the quantity of liquid injected and of the five days of starvation. He reports the injection of 50 to 90 cc., which would probably dilute the blood considerably and also cause a shock to derange the general metabolism. Furthermore, he observed a reduction in sugar in the case of some extracts but was often unable to get a similar result with the same materials in other animals. It appears that the effects obtained were due to the condition of the subject rather than to a specific constituent of the extract. If there was such a constituent, consistent results should be obtained. In the earlier work on insulin an active extract invariably exerted its effect on all animals within six hours. Some of Collip's extracts did not develop a subnormal blood-sugar until five days after injection and, since food was withheld entirely during the course of the experiment, it is obvious that the reduction in sugar was due to starvation.

Thalkimer and Perry (2) noted from 5 cc. of raw potato juice intravenously a reduction of sugar from 0.17 down to 0.13 per cent. They did not state the method of determination but it is evidently one capable of considerable error, or the amount found for normal would not be so high. One experiment only was reported and it would seem inadvisable to draw any exact conclusion therefrom.

Winter and Smith (3) used extracts of yeast from various sources. Of 17 experiments reported, only 3 showed lower than normal amount of blood-sugar and an attempt to repeat one of these resulted in failure.

In view of these facts, our own experiments and a careful survey of other literature, it seems to us entirely reasonable to question the existence of any evidence that plants contain a substance which will alter amounts of sugar in the blood.

SUMMARY.

No evidence could be found for the reputed activity of plant extracts in reducing normal or high blood-sugar. Also no evidence could be found for any transference of hypoglycemia from one animal to another.

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SUGGESTIONS FOR THE IMPROVEMENT OF PROFESSIONAL RELATIONS BETWEEN DENTISTS AND PHARMACISTS.*

BY C. L. WHITMAN, D.D.S.

The professions of Dentistry and Pharmacy have been very closely related since their beginning. It is my purpose to point out some of the reasons for and method by which the pharmacists and dentists may coöperate to their mutual advantage.

In the United States there are about 67,000 dentists, all of whom prescribe drugs to a certain extent. But as a rule, while drugs are used often they are not prescribed as effectively or skilfully as they might be. I do not mean to condemn the dental profession as a whole, but this condition exists more frequently than it should. Dentistry has been practised for centuries but not as we know it to-day; modern dentistry, as a distinct and separate profession, was born in 1839 when the Baltimore College of Dental Surgery, the first dental school in the world, was established in Baltimore. Dentistry and medicine were from that year practically divorced and while dentistry, in its early days, depended largely on medicine for its development, its fundamental studies are at present based on biology, exactly as is medicine or any other branch of the healing art. Before this first dental college was established few specific books on dental therapeutics existed; the little knowledge concerning the action of drugs was scattered through the few dental works which existed at that time, or was closely guarded by its possessors. Since then dentistry has rapidly forged ahead—great strides have been made and dentistry is continuing to progress.

* Section on Education and Legislation, A. P. H. A., Washington meeting, 1934.