Effect of Aspirin Upon Glycosuria of the Partially Depancreatized Rat. (18301)

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The data of this report show that large doses of aspirin (acetylsalicylic acid) suppress the glycosuria of the partially depancreatized rat.

Methods. Male rats of the Sprague-Dawley strain were subjected to partial pancreatectomy(1) at a weight of approximately 300 g. Following recovery from the operation, the animals were placed in metabolism cages and were force-fed a medium carbohydrate diet (2) by stomach tube each morning (8:30 to 9:15 A.M.) and afternoon (4:15 to 5:00 P.M.). Twenty-four-hour samples of urine were collected at the same hour (8:00 to 8:30 A.M.) and were preserved with toluene. Urine glucose was determined by the method of Benedict(3). Aspirin was ground into a fine suspension in peanut oil at a concentration of 100 mg per cc. It was administered by subcutaneous injection in divided doses each morning and late afternoon.

Results. Seven mildly diabetic rats were observed during a control period of several weeks. During the daily administration of 40, 80, and 160 mg of aspirin for one week, at each dose level, there was a marked decrease in the glycosuria in each animal at each dose level together with a concomitant gain in weight. In each rat, the quantity of reducing substances in the urine was depressed below 200 mg on one or more days during treatment with aspirin. When the injections of aspirin were stopped, there was an exacerbation of the glycosuria to levels much higher than were observed during the initial control period, and there was an accompanying loss of weight. The data are summarized in Fig. 1.

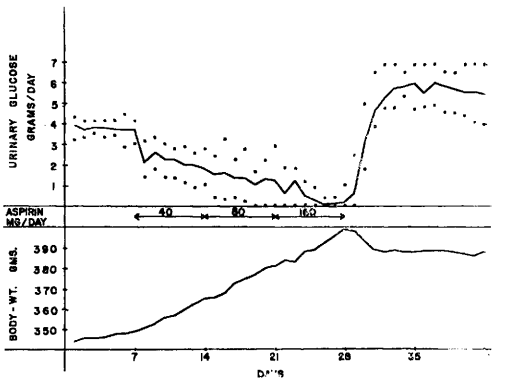

FIG. 1.

Effect of aspirin upon the urinary glucose and body weight of 7 partially depancreatized force-fed rats. Averages and range.

Discussion. In this laboratory, we search for compounds which modify experimental diabetes. Aspirin and cortisone each suppress the symptoms of rheumatoid arthritis. Cortisone causes exacerbation of diabetes in mildly diabetic animals. This was the basis for speculating about the effect of aspirin upon the level of glycosuria in such animals. The effect of aspirin in ameliorating the glycosuria is unlike the effect of cortisone. The mechanism of its action and its possible relationship to the function of the adrenal cortex are unknown. It is interesting to note that the effect of aspirin upon glycosuria is as marked as the ameliorating effect of adrenalectomy in our experience(4).

The possibility that aspirin may conjugate with glucuronic acid and be excreted in a form which would not be detected by tests for reducing substances has been pointed out to us. Since the possible conjugation would be molecule per molecule, the amount of aspirin administered could not mask the excretion of more than an equivalent weight of reducing substances. This would represent a very small fraction of the actual decrease in urinary reducing substances during treatment with aspirin.

1. Ingle, D. J., and Griffith, J. Q., Surgery in the Rat, Ch. 16 in *The Rat in Laboratory Investigation,* Philadelphia, J. B. Lippincott Co., 1942, p.434-451.

2. Ingle, D. J., Nezamis, J. E., and Rice, K. L., *Endocrinology,* 1950, v46, 505.

3. Benedict, S. R., *J.A.M.A.,* 1911, v57, 1193.

4. Ingle, D. J., and Prestrud, M. C., *Am. J. Physiol.,* 1948, v152, 603.

The amount of aspirin required to ameliorate the glycosuria of the rat is very large, and there is no reason to expect that this drug would be of any therapeutic value in clinical diabetes.

Summary. Aspirin was administered to 7 mildly diabetic rats which were force-fed a medium carbohydrate diet. The dose was 40, 80, and 160 mg of the drug per day. A marked amelioration of the glycosuria together with a gain in weight was noted in each rat. When the drug was withdrawn, there was exacerbation of the glycosuria to significantly higher levels than were noted during the preinjection period, and there was an accompanying loss of weight.

Addendum. Since this manuscript was submitted for publication a review (Gross, M. and L. A. Greenberg, Hillhouse Press, New Haven, Conn., 1948. pp 108-9) of the effects of salicylates upon carbohydrate metabolism has been noted. Salicylates were shown to have an ameliorating effect upon diabetes mellitus in man as early as 1875, but large and frequently toxic amounts were required and the use of salicylates for this purpose has long since been discontinued. The nature of the action of salicylates upon carbohydrate metabolism remains as an interesting problem.

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A New Criterion for Anti-tumor Activity of Tissue Extracts Using Crocker Sarcoma No. 180 in Mice.* (18302)

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When Crocker Sarcoma No. 180† is implanted into CFW male mice (Carworth Farms), a loss in weight of the animals invariably occurs on the 7th or 8th day following implantation at a time when the tumors are in rapid growth. One is tempted to regard this loss in weight as concurrent with the development of a cachectic state, somewhat analogous to what occurs in advanced human cancer cases. Apparently most of the transplantable tumors fail to show the same behavior. We have investigated in this respect, the Walker Carcinosarcoma 256 transplanted into Sherman, Wistar and Sprague-Dawley rats, Mammary Adenocarcinoma E.O. 771 transplanted into C-57 female mice (Rockland Farms), a spontaneous mammary tumor (Cystoadenocarcinoma) found in Swiss Webster female mice (Rockland Farms) and in fewer instances in the Rous Sarcoma of chickens. All these tumor strains showed either no loss in weight, due to the tumor, or this occurred only in some cases. It seems, however, possible that some other tumors may be found, in which this phenomenon can be demonstrated.

We have used the above tumors for routine assay of extracts obtained from various organs in assaying the potency of tumor-inhibiting and tumor growth-stimulating activity. Some 130 experiments were performed in the last 3 years in this direction. When we used such active fractions in the first mentioned tumor (Crocker Sarcoma No. 180) we found invariably, that while control animals showed a loss in body weight, tumor-growth-inhibiting fractions (in doses 5-10 mg/mouse, total dose 40-80 mg) caused body weight increases, while tumor-stimulating fractions showed even larger weight losses than the controls (Fig. 1) Normal controls, not bearing the tumor, gain on an average 10 g during the experimental

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† The spontaneous tumor used was obtained from Rockland Farms. Rous Sarcoma was kindly supplied to us by Dr. A. Claude, of the Rockefeller Institute, N. Y., all the other tumors used in this work were most generously made available by Dr. K. Sugiura, Sloan-Kettering Institute, N. Y., to whom our sincere thanks are due.