Comparison of Pancreatic and Steroid Diabetes in Respect to Tumor Growth and Glycosuria

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SUMMARY

Sexually mature male rats were made severely diabetic by either pancreatectomy or daily injection of large doses of cortisone acetate. One half of the animals were then made host to Walker Carcinoma 256. The tumor suppressed the glycosuria in all of the animals, but the effect was greater in steroid diabetes than in pancreatic diabetes. Diabetogenic doses of cortisone inhibited the growth of tumor to a greater extent than did pancreatic diabetes. The depancreatized tumor host is partially resistant to the diabetogenic action of cortisone. DIABETES *14*:93-95, February 1965.

Walker Carcinoma 256 suppresses glycosuria in depancreatized rats[1] and in rats with steroid diabetes.[2] In the present experiments the growth of tumors and the effect of the tumor on glycosuria were compared in depancreatized rats and in rats having equally severe glycosuria induced by cortisone. Diabetogenic doses of cortisone inhibited tumor growth to a greater extent than did pancreatic diabetes. In rats with steroid diabetes the tumor, although much smaller, suppressed the glycosuria to a greater extent than in depancreatized rats. Administration of cortisone to depancreatized tumor hosts caused some increase of glycosuria but the response was small.

METHODS

Male rats of the Sprague-Dawley strain were subjected to extensive partial pancreatectomy at weights of 300 to 320 gm. The procedure of Ingle and Griffith[3] was modified to remove pancreas between the bile duct and duodenum by aspiration with a fine pipette. Almost all pancreas can be removed from a rat of any size within ten minutes. If pancreatectomy is "complete" the animal must be treated with insulin in order to survive. In these experiments approximately 3 per cent of the entire pancreas was left in the area of the bile duct. Such animals begin to excrete glucose as soon as they regain appetite following operation, but treatment with insulin is not required for survival. Approximately six weeks following operation they were placed in metabolism cages and adapted to the force-feeding of a medium carbohydrate diet[4] each morning and late afternoon (26 cc. per rat per day). Intact rats of the same weight range were also placed in metabolism cages and adapted to tube-feeding. Steroid diabetes was induced by the subcutaneous injection of 15 mg. of cortisone acetate (Upjohn) in aqueous suspension following each morning feeding. All of the rats received daily subcutaneous injections of penicillin (5,000 U.) and streptomycin (5 mg.). Twenty-four-hour samples of urine were collected each morning just prior to feeding, and urinary glucose was determined by the Technicon AutoAnalyzer. This requires measuring the creatinine and uric acid of urine. These are also reducing substances, and subtracting the values from total reducing substances gives approximate values for urinary glucose.

After the values for urinary glucose had become stable for the depancreatized rats, and after steroid diabetes had reached peak severity in the intact rats (one week after starting injections), half of the rats of each group received injections of sterile undiluted homogenate of Walker Tumor 256 into the upper thigh of each hind leg. At the end of the experiment each rat was exsanguinated under deep ether anesthesia and the tumor was dissected free and weighed.

EXPERIMENTS AND RESULTS

Experiment 1 (figure 1) involved twenty severely diabetic depancreatized rats. Ten rats were made hosts to tumor. By six days after implantation of tumor, the average glycosuria fell below that of the controls and continued to decline to an average of about 2 ± 0.43 S.E. gm. by the twenty-first day as compared to an average of about 6 ± 0.25 gm. per day for the controls. Average weight of tumors in diabetic rats was 64.2 ± 5.4 gm. compared to 82.9 ± 2.4 gm. for twelve nondiabetic tumor hosts kept under identical conditions.

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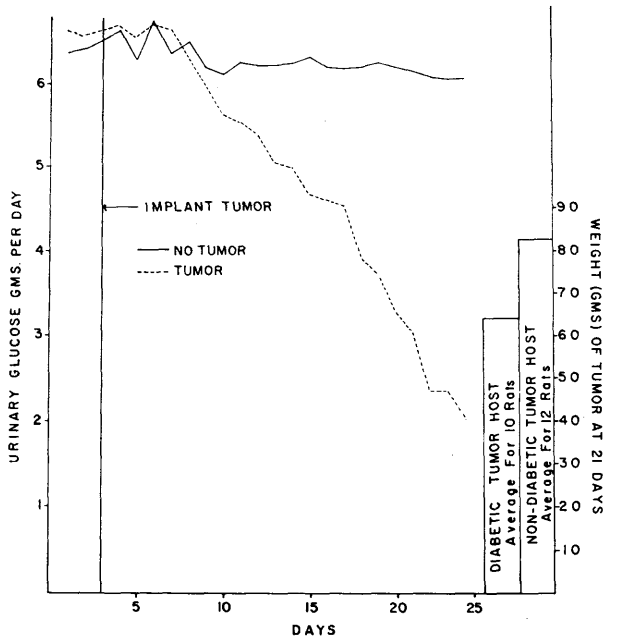

FIG. 1. Effect of Walker Carcinoma 256 on the glycosuria of depancreatized (tube-fed) male rats. Averages for ten rats per group.

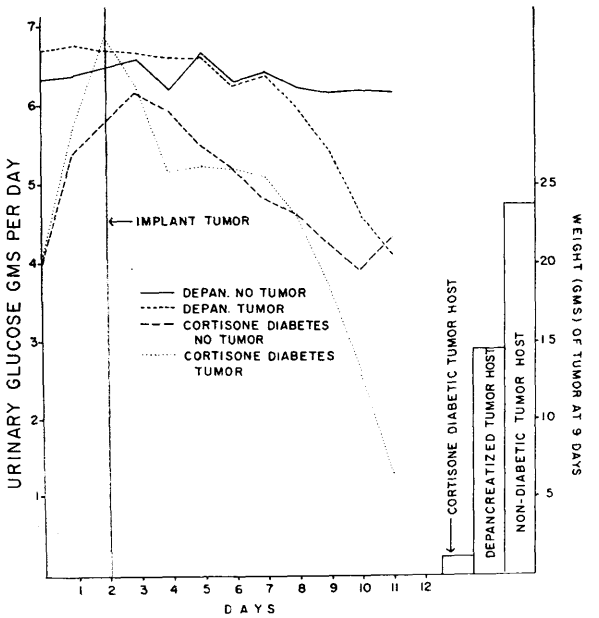

FIG. 2. Effect of tumor on the glycosuria of rats having pancreatic diabetes and rats having steroid diabetes (cortisone acetate, 15 mg. daily) from day 0. Averages for eight rats per group.

Experiment 2 (figure 2) involved sixteen depancreatized rats and sixteen intact rats with steroid diabetes. Half of the animals of each group were implanted with tumor when the glycosuria was at peak severity, and all animals were autopsied nine days later. Here again the tumor suppressed the glycosuria of depancreatized rats below that of depancreatized rats without tumor. The glycosuria of rats with steroid diabetes falls spontaneously from an early peak, but the fall was accelerated by the presence of tumor although the average weight of tumor at the end of nine days was only 1.1 ± 0.06 gm. Under identical conditions the average weight of tumor in rats having pancreatic diabetes was 8.6 ± 1.3 gm. and the average weight of tumor in eight nondiabetic tumor hosts was 23.9 ± 2.8 gm.

Experiment 3 (figures 3 and 4) was a test of the effect of cortisone on the glycosuria of severely diabetic rats in which the glycosuria had become mild due to the presence of tumor. Five rats were treated with cortisone after the initial glycosuria of over 6 gm. per day had been suppressed to less than 1.5 gm. of glucose per day; five similar rats were kept as controls. All of the rats died within nine days, due to the mass of tumor and its metastases. Although depancreatized rats without tumor are highly sensitive to cortisone, the glycosuric response of these tumor hosts was small.

Attempts to study steroid diabetes and the effect of

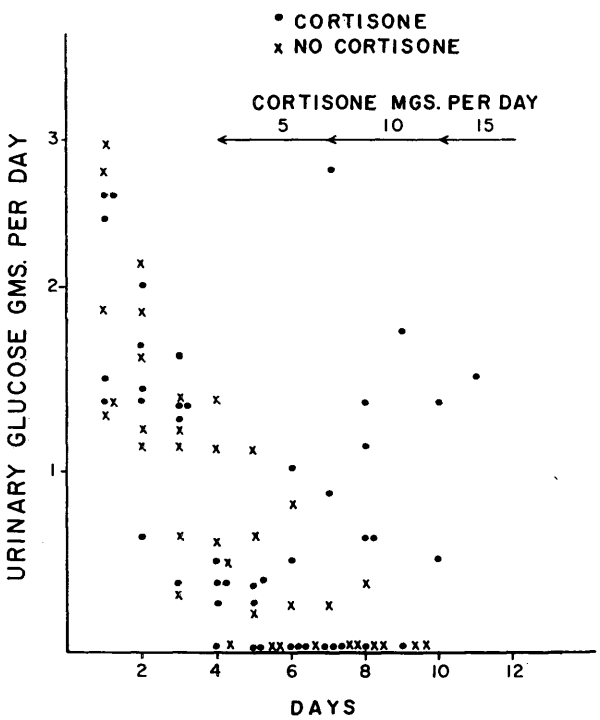

FIG. 3. Mild exacerbation of glycosuria in five depancreatized rats having initial glycosuria of 6 or more gm. per day suppressed by tumor. Individual values shown to death of animals.

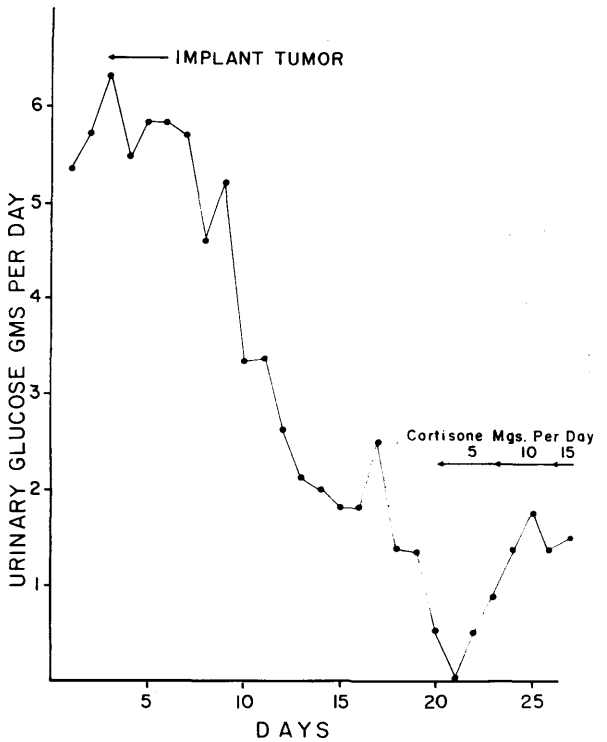

FIG. 4. Illustration of mild exacerbation of glycosuria by cortisone in a depancreatized tumor host.

tumor upon it in adrenalectomized-depancreatized rats normalized by treatment with insulin and adrenal cortex extract were unsuccessful. It is difficult to keep the urine of such tube-fed animals sugar-free without causing hypoglycemic shock. When steroids were administered to animals with diabetes caused by pancreatectomy and which was previously controlled, a severe diabetic state was easily reinduced. The animals commonly developed fatal acidosis, however, without severe glycosuria; when the animals survived, the glycosuria tended to decrease rapidly.

DISCUSSION

The mechanism by which tumor suppresses glycosuria in the rat is not known. Since the diabetic tumor host has two wasteful pathologic processes competing for calories and for protein it is not surprising that each disease is modified by co-existence with the other. In the depancreatized rats the tumor grows to a size which may utilize significant amounts of glucose. It is difficult to explain the effect of the tumor on steroid diabetes; the glycosuria can be markedly suppressed by a very small tumor which appears almost completely necrotic. It seems probable that some of the effects of the tumor are systemic and are not limited to processes occurring within the tumor. David Ingle[5] has shown that other stressors suppress steroid diabetes in the rat. Some stressors tend to suppress pancreatic diabetes in the rat,[6] others do not significantly affect it, and still others cause exacerbation of glycosuria. Ingle has suggested that severe stress might be expected to suppress the symptoms of hypercorticalism,[5] but tests[7] of this hypothesis have been largely negative. The adrenal cortices of rats which are host to Walker Carcinoma enlarge markedly, up to ten times normal weight. The hypertrophy can be suppressed by exogenous cortisone. Does the hypertrophy occur in response to an increased "need" for steroid, because the tumor is stressful or because it interferes with the synthesis or utilization of steroid? Establishing the role of adrenal hormone production and utilization in the tumor host is one of several facets of this problem which will require more penetrating study.

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