line with the prior suggestion(8) that endotoxin triggers the release of intracellular factors of which a DD-like material is only one, the factors responsible for early effects on clearance being absent in the case of DD administration.

It has also been suggested previously(8) that the release of stimulatory oligodeoxyribonucleotides may be a natural event, possibly as a consequence of interactions between antigen and antibody on cell surfaces. In view of the present data it can now be suggested that such stimulators may affect not only the multiplication and functioning of antibody-forming cells, but also the activity of cells involved in the uptake and processing of the antigen.

Summary. Oligodeoxyribonucleotides (but not monodeoxyribonucleotides), derived from calf thymus DNA, produce a significant stimulation of the phagocytic activity of the reticuloendothelial system. Kinetin riboside inhibits this stimulation without affecting the normal rate of clearance. This reversal of the effects of oligodeoxyribonucleotides is comparable to that previously observed in studies on stimulated antibody formation.

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Effect of Jensen Tumor on Pancreatic Diabetes in Nonadrenalectomized and Adrenalectomized Rats.*† (30493)

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The author is among several who have reported that certain tumors suppress the glycosuria of diabetic rats and other animals (1). The effect is more striking in steroid diabetes than in pancreatic diabetes(2). The adrenal cortices of the tumor host enlarge several-fold, yet the glycosuria is ameliorated, not exacerbated as would be expected if the tumor caused a state of hypercorticalism. If the adrenals of the tumor host should be incapable of secreting normal amounts of glucocorticoids, this might explain the suppression of glycosuria as due to hypocorticalism and the cortical hypertrophy as a compensatory response to hypocorticalism. A partial test of this hypothesis herein reported, shows that Jensen sarcoma suppresses the glycosuria of adrenalectomized rats given "normalizing" doses of adrenal cortex extract, therefore modification of secretion of corticoids cannot be the only way in which the tumor affects the glycosuria.

Methods. Male Sprague-Dawley rats were partially pancreatectomized at a weight of 275-285 g. The procedure of Ingle and Griffith(3) was modified to remove the pancreas lying between the bile duct and duodenum by gentle aspiration with a fine pipette. Any amount of pancreas can be removed within 10-15 minutes.

Extensive but not "complete" pancreatectomy was done on some animals and 85 to

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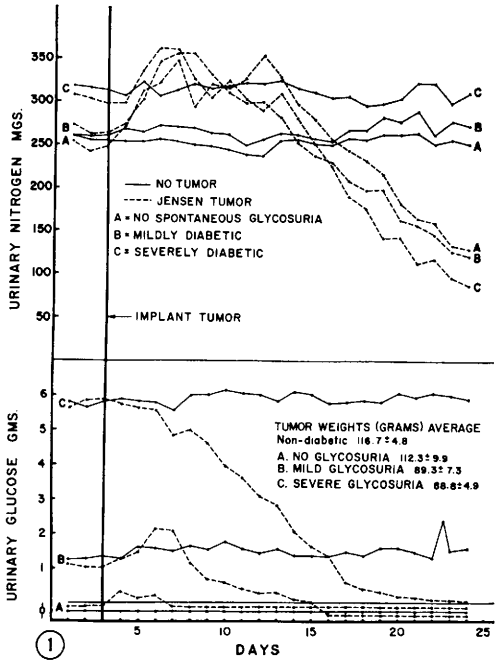

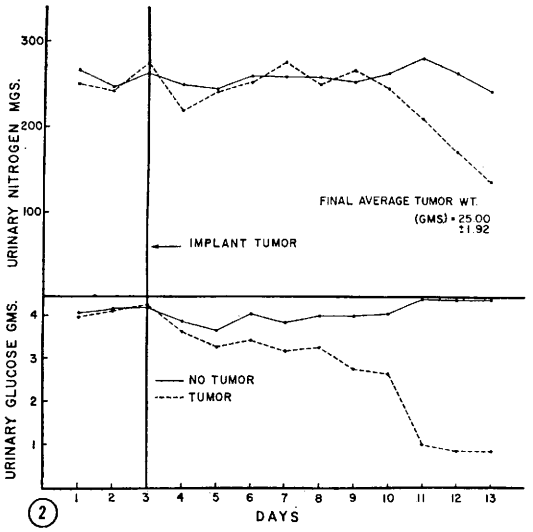

FIG. 1. Effect of Jensen sarcoma on urinary glucose and nitrogen of partially depancreatized rats having intact adrenals. Averages for 6 tube-fed rats per group.

FIG. 2. Effect of Jensen sarcoma on urinary glucose and nitrogen of adrenalectomized-depancreatized rats treated with 2 ml of adrenal cortex extract per rat per day. Averages for 6 tube-fed rats per group.

95% of pancreas was removed from others. Post-operative treatment with insulin was not required but would be required after "complete" pancreatectomy. During the first 7 days, all rats were given 5000 U of penicillin and 5 mg of streptomycin per rat per day. Adrenalectomy was by the usual dorsal approach, using clean technique. The animals were treated with beef adrenal extract (ACE) in divided doses each morning and late afternoon.

After 6 weeks, the rats were placed in metabolism cages and adapted to the tube-feeding of a medium carbohydrate diet(4) each morning and late afternoon (26 cc per rat per day). 24-hour samples of urine (kept acid by 1 g of citric acid per sample) were collected at 8:30 to 9:00 AM and preserved with thymol. Urine glucose and nitrogen were determined by the Technicon AutoAnalyzer. Creatinine and uric acid of urine were determined separately and the values subtracted from total reducing substances, giving approximate values for urinary glucose. Undiluted homogenate of tumor was injected into the upper thigh of each hind leg. At the completion of each experiment, the rats were anesthetized with ether, exsanguinated and the tumors dissected free and weighed.

Experiments and results. There were 12 rats in each of the following groups of Experiment 1 (Fig. 1): A, no glycosuria; B, mild glycosuria; and C, severe glycosuria. Six rats in each group were implanted with Jensen sarcoma and observed for 21 days. Some of the rats in groups A and B showed slight exacerbation of glycosuria for about 3 days. and thereafter it decreased to zero or almost zero in all tumor hosts. Implantation of tumor caused a temporary rise in urinary nitrogen in each group, but as the tumor became large, urinary nitrogen was markedly decreased. The average weight of tumor showed a negative correlation with the severity of the glycosuria. Fig. 1 includes an average value for tumor weights of 12 non-depancreatized rats.

Experiment 2 (Fig. 2) involved 12 severely diabetic rats that were adrenalectomized and treated with 2 ml of ACE per rat per day.

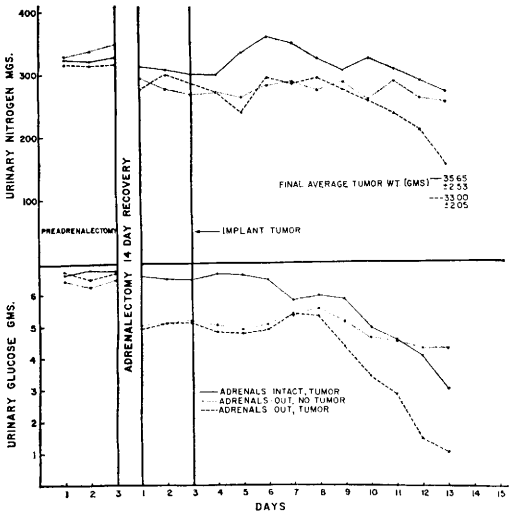

FIG. 3. Comparison of effect of Jensen sarcoma in adrenalectomized-depancreatized rats having intact adrenal glands. Averages for 6 tube-fed rats per group.

The preadrenalectomy glycosuria averaged over 6 g per day but decreased about 2 g per day following adrenalectomy. There was an accompanying decrease in urinary nitrogen. Preadrenalectomy values of glucose and nitrogen are not shown in the Figure. After a 14-day recovery period, 6 adrenalectomized-depancreatized rats were implanted with tumor and observed for 10 days before necropsy. Longer periods were attempted, but such animals do not survive as well as non-adrenalectomized animals, and also the effect of the tumor is clearly established within 10 days. The tumor caused a marked decrease of urinary glucose and nitrogen in the absence of the adrenal glands.

Experiment 3 (Fig. 3) involved 18 severely diabetic rats: 6 non-adrenalectomized and 12 adrenalectomized. All adrenalectomized rats were treated with 3 ml ACE per rat per day. After a 14-day recovery period, 6 adrenalectomized-depancreatized rats were implanted with tumor and observed for 10 days before necropsy. Following adrenalectomy, the levels of urine glucose and of nitrogen decreased, which means that the dose of ACE, although large, did not fully replace the effects of the animal's own adrenal hormones upon organic metabolism. The tumor caused a marked decrease of urinary glucose and nitrogen.

Discussion. The tumors grew at a nearly normal rate in depancreatized rats without glycosuria but growth was suppressed in diabetes to an extent correlated with the severity of glycosuria. As the tumor grew, the glycosuria fell to a low level and was abolished in most animals within 21 days. There was an accompanying decrease in urinary nitrogen.

Jensen sarcoma also suppressed the levels of urinary glucose and nitrogen in the absence of the adrenal glands and in the presence of a steady intake of cortical extract. The hypothesis that the tumor suppresses glycosuria by causing a state of hypocorticalism cannot be the complete explanation for the amelioration of diabetes in the tumor host. It is possible that the tumor greatly increases the "need" for glucocorticoids and that a state of relative adrenal insufficiency develops despite a steady intake of ACE. There are other hypotheses which have not been fully tested. Possibly these tumors secrete insulin or other substances affecting diabetes. Tumors are known to oxidize glucose at high rates; these large tumors may utilize significant amounts of glucose in the absence of insulin. The neoplastic tissue and the diabetic state compete for proteins of the diet and tissues. The elevated rate of protein catabolism and gluconeogenesis in diabetic animals is suppressed by the rapidly anabolizing tumor. It is necessary to explain the disappearance of as much as 6 g and more of urinary glucose per rat per day in the severely diabetic animals of Experiment 1. There may be more than one mechanism causing the suppression of glycosuria by Jensen sarcoma.

Summary. Jensen sarcoma caused a striking decrease in the glycosuria of extensively depancreatized male rats in the presence of the adrenal glands and in adrenalectomized-depancreatized rats treated with adrenal cortex extract. There was an accompanying decrease in the level of urinary nitrogen. The rate of tumor growth was inversely related to the severity of pancreatic diabetes.

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Neoplastic Changes in Pituitary Intrarenal Isografts in Mice. (30494)

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One of the effective means of tumor induction in the pituitary gland is by sustained interference with the physiological homeostatic equilibrium of that organ—*e.g.*, (a) induction of functioning thyrotropic pituitary tumors *in situ* by destruction of the thyroid gland or by blocking its normal functioning (1), and (b) induction of various types of tumors in isografts of pituitary gland, *i.e.*, after transplantation at sites remote from hypothalamic influence(2,3,4). It so happens that such isografts continue secreting large amounts of prolactin(5), though no appreciable amounts of other tropic hormones; and as a consequence, mammary glands undergo early hyperplastic changes and later, neoplastic changes(2). Regarding the characterization of types of neoplasms produced in the pituitary gland, methods have been developed (originally in connection with pituitary tumor induced by ionizing radiation) by bioassay techniques for distinguishing thyrotropic, mammotropic and adrenotropic tumors (6).

In our studies on the role of hormones in mammary tumor development(7,8), the technique of pituitary intrarenal isografts was used as a means for endogenous, continuous prolactin secretion. Many of these pituitary isografts became transformed after a long latent period into pituitary tumors.

The aim of the present study was to analyze the type of these pituitary tumors by transplantation bioassays in isologous hosts.

Materials and methods. Mice of the genetically uniform (C57L × A/He)F_1 strain inbred in our laboratory were used in these experiments at about 6-8 weeks of age. They were fed Purina Laboratory Chow and water *ad libitum*. Female mice received isografts of a single pituitary gland beneath the left kidney capsule through an 18-gauge hypodermic needle fitted with a metal plunger. The pituitary gland donor mice of 2 age groups—60-day and 300-day-old were of the same sex as the recipients. One small group of male mice received a pituitary renal implant from 60-day-old female donors.

Eight of the primary pituitary tumors were bioassayed by retransplantation of tumor tissue beneath the kidney capsule of normal hosts.

Results. The pituitary intrarenal graft tumor incidences in the different treated groups are summarized in Table I. Of the pituitaries grafted beneath the kidney capsule of female hosts, 60-80% showed progressive growth, suggesting neoplastic transformation. The female mice bearing pituitary graft tumors also showed marked mammary gland hyperplasia, while all the other organs appeared normal. The intact pituitaries of these mice were also normal. In a small group of 6 males grafted intrarenally, 2 of the grafts (from female donors) developed into tumors. These males showed grossly very enlarged seminal vesicles, while the other

TABLE I. Pituitary Tumor Development in Intrarenal Isologous Pituitary Grafts.

Age of pituitary donor (days)	Mice bearing tumors /survivors	% Pituitary tumors	Avg age of tumor-bearing mice (days)
60	24/30 ♀	80	600
60	2/6 ♂	33	665
300	13/22 ♀	60	420