rated fat showed a significant creatinuria. Depletion of the saturated fat-fed group to an average tissue α-tocopherol level of 0.4 μg/g did not produce creatinuria.

1. Witting, L. A., Horwitt, M. K., J. Nutrition, 1964, v82, 19.
2. ———, ibid., 1964, v84, 351.
3. ———, Proc. Soc. Exp. Biol. and Med., 1964, v117, 320.
4. Witting, L. A., Fed. Proc., 1965, v24, 912.
5. ———, J. Am. Oil. Chem. Soc., 1965, v42, 908.
6. Mameesh, M. S., Johnson, B. C., J. Nutrition, 1958, v65, 161.
7. Century, B., Horwitt, M. K., ibid., 1960, v72, 357.
8. Woodman, A. G., Food Analysis, ed. 4, McGraw-Hill Book Co., Inc., New York, 1941, p185.
9. Kubin, H., Fink, H., Fette Seifen Anstrich., 1961, v63, 280.
10. Emmerie, A., Engel, C., Rec. trav. chim. Pays-Bas, 1938, v57, 1351.
11. Bonsnes, R. W., Taussky, H. H., J. Biol. Chem., 1945, v158, 581.
12. Lundberg, W. O., ed., Autoxidation and Antioxidants, v1, Interscience Publishers, New York, 1961.
13. Horwitt, M. K., Fed. Proc., 1965, v24, 63.
14. Witting, L. A., submitted for publication.

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Species Difference in Hormonal Control of Intestinal Weight and Food Intake of Rats and Pigeons. (30636)

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Bates *et al*(1) have shown in hypophysectomized pigeons that replacement therapy with a combination of four pituitary hormones, growth hormone, prolactin, TSH and ACTH, caused a large body weight gain and food intake, and larger than normal organ to body weight ratios for the intestine, liver, kidney and pancreas. These data indicated a specific effect of the exogenous hormones on the size of these organs. Later studies by Milkovic *et al*(2) in rats with mammotropic tumors, MtT, suggested that the high levels ($>$30 times normal) of growth hormone, prolactin and ACTH in the blood of these rats did not specifically enlarge the intestine and pancreas, yet they caused large livers, kidneys and hearts.

There is a paucity of data in the literature in which both food intake and intestinal size have been measured. This paper presents a look at certain accumulated data in rats and pigeons where both empty gut weight and food intake were measured.

Methods and materials. The transplantable pituitary tumor, used in these studies, was the mammotropic tumor (MtT), strain F4, which was grown in Fischer rats and was originally obtained from Dr. Furth. We have had it for over 35 transfers. Most of the data here was from our transfers 20 to 30. The tumor had a latent period of growth of about 30 days. Fischer rats about 4 to 6 months old were used throughout. The pigeons were all 6-8 weeks of age of the white Carneau strain.

Most of the rat data is from a study to be published on the induction of diabetes in partially pancreatectomized rats. The percentage of the pancreas removed was checked by weighing the pieces removed during surgery. Partial pancreatectomy and adrenalectomy was usually done after tumor implantation and before the tumor became palpable and began to produce hormones. Severe diabetes, with blood sugars around 300 mg% and daily excretion of 2 to 5 g of glucose in the urine, developed in most rats with MtT if more than 40% of the pancreas was removed and the adrenals were intact.

The intestines, from the pylorus to the anus in rats and from the gizzard to the cloaca in pigeons, were weighed after removing the contents by stripping and/or cutting (especially the cecum).

Except for fasting or force feeding in a

TABLE I. Relative Size of Gut and Food Intake in Rats With or Without MtT, Diabetes, Adrenals, and With Various Amounts of the Pancreas Removed. Food intakes were *ad libitum* except in the case of fasting. Most tumors had been palpable for 30 days.

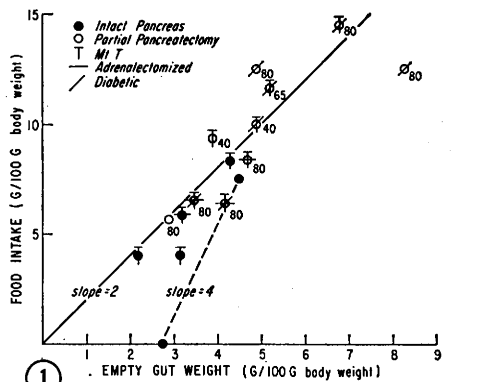
Group		MtT	Diabetic	$\overline{\text{A}}$*	No. rats	Body wt (g)	Tumor wt (g)	Food intake (g/100 g)	Gut wt (g/100 g)	Food intake/gut wt
1	Intact-control	0	—	—	40	163 ± 3	—	7.5 ± .2	4.5 ± .3	1.66
2	Intact-fasted 7 days	0	—	—	5	116 ± 1	—	0	2.8 ± .1	0
3	Intact	+	—	—	14	277 ± 10	28 ± 4	8.3 ± .4	4.3 ± .2	1.93
4	Intact-high fat diet†	+	—	—	5	227 ± 7	19 ± 1	4.0 ± .2	3.2 ± .1	1.27
5	Intact-high fat diet‡	+	—	—	5	248 ± 9	38 ± 4	4.0 ± .2	2.2 ± .2	1.83
6	80% $\overline{\text{P}}$§	0	—	—	4	182 ± 8	—	5.7 ± .2	2.9 ± .1	1.93
7	80% $\overline{\text{P}}$	+‖	+++	—	4	223 ± 20	(15)‖	12.5 ± 2	4.9 ± .5	2.54
8	80% $\overline{\text{P}}$	+¶	+++	—	4	159 ± 7	(3)¶	12.5 ± 1	8.3 ± .3	1.50
9	80% $\overline{\text{P}}$	+	+++	—	6	158 ± 8	16 ± 3	14.5 ± .7	6.8 ± .5	2.11
10	65% $\overline{\text{P}}$	+	+++	—	8	239 ± 10	24 ± 5	11.7 ± 1	5.2 ± .3	2.25
11	40% $\overline{\text{P}}$	+	+++	—	3	265 ± 19	33 ± 6	10.0 ± 1	4.9 ± .2	2.04
12	40% $\overline{\text{P}}$	+	—	—	8	257 ± 10	27 ± 4	9.4 ± .8	3.9 ± .3	2.40
13	Control $\overline{\text{A}}$	+	—	+	4	287 ± 21	11 ± 2	5.9 ± 1	3.2 ± .2	1.84
14	80% $\overline{\text{P}}$	+	+	+	4	308 ± 18	29 ± 4	6.5 ± .3	3.5 ± .3	1.85
15	80% $\overline{\text{P}}$	+	+	+	5	297 ± 7	10 ± 2	6.4 ± .3	4.2 ± .2	1.53
16	80% $\overline{\text{P}}$	+	—	+	4	238 ± 12	8 ± 5	8.4 ± 1.0	4.7 ± .3	1.77

* Rats were adrenalectomized (A) more than 37 days. Given .9% NaCl solution to drink.
† On high fat diet 12 days.
‡ " " " " 26 "
§ Rats were partially pancreatectomized more than 25 days in all cases.
‖ MtT removed after diabetes developed and 23 days before killing.
¶ " " " " " " 16 " " "

few groups of pigeons all food intake of rats or pigeons was *ad libitum* and reflects appetite or hunger induced by the treatment. Food intakes were measured for 24-hour periods a few days before killing by placing rats in metabolism cages with food tunnels especially designed to minimize scattering of the diet. All rats were fed Purina Rat Chow unless indicated otherwise. The high fat diet contained 40% fat(3). At the time of killing all groups of rats had been 2 or more weeks under treatment with the exception of the fasting group. Food intakes are expressed as grams/100 g body weight. Body size differed by a factor of more than 2 among different groups of rats but not within groups. None of the rats in any group had more body fat than the normal group. In fact most of the rats with tumors had no depot fat. Body weights of pigeons differed usually by no more than 25%.

Results. Intestinal size in the rat. Table I lists the various operations and conditions which influenced the voluntary food intake and intestinal weights of the Fischer rats. Most groups had MtT. Many groups were partially pancreatectomized ($\overline{\text{P}}$) to the extent indicated. The ratio of food intake to gut weight is shown in Table I and is roughly 2 except for the fasting group. The food intake data from this Table are plotted against the weight of the empty gut in Fig. 1. A high correlation between food intake and gut weight is apparent. An arbitrary line which has a slope of 2 and passes through the origin has been drawn through the data. This would suggest that in the rat the gut increases about 1 g in weight for every 2 g of food eaten with the exception of fasting. A line drawn between the points for fasting and fed normal rats has a slope of 4.

The groups of rats fell into 3 classes on the basis of gut weight. All 5 points with the largest gut weights (>4.8 g/100 g) and food intakes are from the diabetic rats (groups 7, 8, 9, 10, 11), which had blood sugars around



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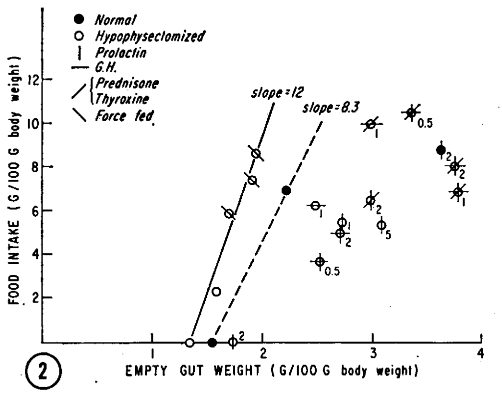

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FIG. 1. Daily food intake and gut weight of groups of rats treated as indicated. Data from Table I, numbers by points indicate percentage of pancreas removed surgically.

FIG. 2. Daily food intake and gut weight of groups of pigeons with and without 10 days treatment as indicated. Numbers by points indicate mg of growth hormone and/or prolactin injected daily. 1 mg prolactin—20 I.U.; Prednisone—1 mg/day; Thyroxine—10 μg/day.

300 mg% and excreted 2 g or more of glucose daily in the urine. In the middle range with gut weights between 3.8 and 4.8 g/100 g are the normal rats, the intact rats with tumors and those partially pancreatectomized groups that did not develop diabetes (groups 1, 3, 12, 16). The rats with small gut weights (<3.8 g/100 g) were 80% $\overline{\mathrm{P}}$ without tumor and not diabetic, were on a high fat diet or were adrenalectomized with MtT, 80% $\overline{\mathrm{P}}$ and slightly diabetic (groups 4, 5, 6, 13, 14, 15). The data for the rats fasted for 10 days naturally must deviate from the line drawn because the food intake was 0.

It is apparent from Fig. 1 that rats having tumors may have either large or small gut weights. Hence the weight of the gut is related to food intake and bears no relation to the high concentration of hormones produced by the tumor. The amount of food passing through the gut is the major factor determining its size. The largest gut weights were in 80% $\overline{\mathrm{P}}$ diabetic rats (Groups 7, 8) which had had MtT but whose tumors were removed after the diabetes became permanent. Hence, these rats did not have high blood levels of pituitary hormones. There is no evidence from bioassays that the blood levels of the hormones from the tumors differ sufficiently to explain the differences in gut weight(2).

Intestinal size in the pigeon. Data on gut weight and food intake from two studies(1,4) of hormonal effects in pigeons are plotted in Fig. 2. Two major differences from the rat studies are that most of the pigeons were hypophysectomized and the treatments, started at the time of hypophysectomy, were injections of exogenous hormones for only 10 days. All of the control data were plotted, but only data from high dose levels of hormones were plotted. The low and intermediate dosage level data would simply grade into the control data.

The slopes of the 2 lines drawn through the control data in Fig. 2, which express the effect of food intake on gut weight, are 8.3 for intact pigeons and 12 for hypophysectomized pigeons. The slopes for intact and hypophysectomized pigeons are of similar magnitude but are greatly different from the slopes of 2 and 4 for the rat (Fig. 1). The displacement of the line through the points for intact pigeons to the right of the line for hypophysectomized pigeons probably represents an effect of endogenous pituitary hormones. Injections of prolactin or growth hormone alone or together clearly increased gut weight out of proportion to food intake by a factor approaching 2. This was especially true of the mixtures of GH, prolactin, thyroxine and prednisone. One group of intact pigeons injected with prolactin is included.

Discussion. The blood levels of GH, prolactin and ACTH in rats with MtT are <30 times those in normal rats(2,5). Without the large effects produced in the host rat by hormones from the MtT the large differences found in these studies in rats would not have been possible. Most of this rat data was obtained along with studies on the induction of diabetes, after partial pancreatectomy, by the hormones from MtT. One might argue that the large intestines of diabetic rats were due to the diabetes and not to the food intake. But in view of all the data here on rats which show an obvious relation between food intake and gut weight it seems probable that the diabetes, which causes a wastage of glucose in the urine, results in an increased food consumption. The body adapts to the increased food intake by increasing gut weight in spite of the diabetic state. The data from rats on a high fat diet suggest that the bulk of the diet and not the caloric content is of greater importance.

Bates *et al*(6) injected the pituitary hormones separately and together at high dosage levels of 10 mg/day into intact rats. GH and prolactin increased the relative empty weight of the gut and ACTH decreased it. A mixture of all 3 hormones caused an intermediate value. Since food intake was not measured it is not known whether or not food intake might have accounted for the differences in gut weight.

Many factors directly or indirectly modify the weight or size of the intestine. The data in this paper indicate that food intake or bulk is a most important factor in the rat. On the other hand the hormones from the anterior pituitary, especially GH and prolactin, are most important factors in the pigeon and food intake plays a minor role.

This dichotomy between the gut response to hormones in pigeons and rats also extends to the weight of pancreas(2). Why these two organs should be divorced from hormonal control in rats and not in pigeons is inexplicable at this time, except as a species difference.

Summary. In rats voluntary daily food intake per 100 g body weight varied by a factor of 4-fold, from 4 g in rats with mammotropic tumors (MtT) on a high fat diet to 15 g of regular rat chow in 80% pancreatectomized rats with MtT and diabetes. The weight of the empty intestine per 100 g body weight varied proportionally and was independent of the high blood levels of pituitary hormones from MtT. The empty intestinal weight was roughly one-half of the weight of the daily food intake in all rats whether partially pancreatectomized, adrenalectomized, diabetic or normal. In pigeons the intestinal weight is not changed much in weight by merely altering food intake, and its weight is nearly doubled by injections of 1 to 5 mg of growth hormone or prolactin daily or equivalent without change in food intake. No explanation other than species difference for these results is possible from the current data. These experiments suggest that food intake data studies are a necessary supplement to intestinal weight studies.

1. Bates, R. W., Miller, R. A., Garrison, M. M., Endocrinology, 1962, v71, 345.

2. Milkovic, S., Garrison, M. M., Bates, R. W., ibid., 1964, v75, 670.

3. Simon, E., Scow, R. O., Chernick, S. S., Am. J. Physiol., 1961, v201, 1073.

4. Schooley, J. P., Riddle, O., Bates, R. W., Am. J. Anat., 1941, v69, 123.

5. Bates, R. W., Milkovic, S., Garrison, M. M., Endocrinology, 1962, v71, 943.

6. ———, ibid., 1964, v74, 714.

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