TABLE III. Effect of Melatonin on Thyroxine Secretion Rate (TSR) in Immature Rats.

Treatment	No. of animals	Body wt (g)	TSR	
			μg L-T_4/100 g BW	Change (%)
Control (.1 mg saline)	16	127.9 ± 2.3	1.53 ± .07	
Melatonin (20 μg/day in .1 ml saline)	17	128.7 ± 2.7	1.28 ± .09	—16.3[1]

All weights accompanied by standard error of mean.
[1] Student's "t" test, P <.025.

While melatonin appears to be concerned primarily with the secretion of the gonadotropic hormones and ovarian development, it may influence other endocrine systems. These effects may be direct or indirect in relation to alterations in feed consumption.

The present study indicates that pinealectomy stimulates feed consumption slightly but not significantly. It was shown also to stimulate an 11.8% increase in TSR.

The slight increase in feed consumption and TSR may explain the favorable effect of pinealectomy upon body growth of rats up to the 14th week reported by Malm *et al*(8).

The administration of 40 μg and 20 μg/day of melatonin had an opposite effect on feed consumption and TSR in comparison with pinealectomy, decreasing feed consumption 12% and TSR 16%.

These data indicate that the absence of melatonin (pinealectomy) tends to increase feed consumption and TSR, whereas melatonin has an opposite effect.

Summary. The effect of pinealectomy upon feed consumption and thyroid hormone secretion rate was studied in Sprague-Dawley-Rolfsmeyer female rats. Feed consumption was increased 5.77% in association with an increase of 11.8% in TSR. In a second group of 16 rats, daily injection of 40 μg/day of melatonin depressed feed consumption 12.0%, whereas injection of 20 μg/day of melatonin into young rats depressed TSR 16%.

1. Wurtman, R. J., Axelrod, J., Chu, E. W., Science, 1963, v141, 277.
2. Wurtman, R. J., Roth, W., Altschule, M. D., Wurtman, J. J., Acta Endocrinol., 1961, v36, 617.
3. Wurtman, R. J., Axelrod, J., Chu, E. W., Ann. N. Y. Acad. Sci., 1964, v117, 229.
4. Fiske, V. M., Lambert, H. H., Endocrinology, 1962, v71, 667.
5. Kitay, J. I., Altschule, M. D., The Pineal Gland, Harvard Univ. Press, Cambridge, Mass., 1954.
6. Grosvenor, C. E., Turner, C. W., Proc. Soc. Exp. Biol. and Med., 1958, v99, 517.
7. Narang, G. D., Turner C. W., ibid., 1966, v121, 203.
8. Malm, O. J., Skang, O. E., Jaerde, P. L., Acta. Endocrinol., 1959, v30, 22.

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Tolerance to Sucrose in Adapted and Nonadapted Rats. (31216)

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While hypertonic solutions of sucrose given intravenously or intraperitoneally are known to produce vacuolizations of the convoluted tubules of the kidney, it is not altogether clear to what extent these morphological changes are involved in the general function of the kidney. From the results of studies on rabbits(1), dogs(2), rats(3) and man(4,5) it appears generally agreed that unless very large doses of sucrose are given at frequent intervals (3-4 days), the development of the tubular vacuolizations does not compromise renal function as it is commonly measured. The time course for the development and regression of renal vacuolization in the rat has been examined histologically(3). In animals injected intraperitoneally with hypertonic sucrose, vacuolizations developed within 3

hours, progressed to a maximum between 6 and 48 hours and were only infrequently apparent after 72 hours. Seven days following the injection no histological evidences of the altered morphology were found.

The present studies were conducted to assess the general status of the adapted animal with respect to the stress incurred by a second loading. If the diminished urine volumes and sucrose excretions observed after a second intraarterial loading(6,7) are interpreted to represent a loss of function (renal or otherwise), greater loads of hypertonic sucrose given during this period might be expected to demonstrate, quantitatively, the animals' decreased resistance to the stress. This was tested by determining the sucrose tolerance in both nonadapted and adapted rats. Additional measurements of urine flow and solute concentrations of urine were made to compare the responses of adapted and nonadapted animals, and to relate these indirect assessments of kidney function to the overall resistance demonstrated.

Methods. Male albino rats (Holtzman, 175-300 g) were used in groups of 8-18 animals each. All animals were prepared, under pentobarbital anesthesia (30 mg/kg), with a chronically indwelling catheter at least 4 days prior to testing. The catheter was advanced through the left common carotid artery and positioned so that its tip rested in the aortic arch. All sucrose loads were administered intraarterially (2 ml/min) by adjusting the infusion volume of a 1.46 M (50% w/v) solution of sucrose. Food and water were allowed *ad libitum* up to the time of the trial; neither was given during the 6-hour test period. All trials were conducted at the same time of day to eliminate diurnal variation. At the time of loading, animals were unanesthetized and restrained in a device that permitted quantitative collection of urine(8).

In the first series of experiments 6 groups of animals were infused (2 ml/min) with sucrose loads between 2.0 and 4.5 ml/100 g body weight (b.w.). This series constituted the once-loaded or nonadapted animals. A second series of animals, made up of 7 groups, was loaded with an adapting dose of sucrose (2.0 ml/100 g b.w.) and restrained for 6 hours. Following this initial exposure to sucrose, these animals were returned to individual cages and allowed food and water *ad libitum* until normal hydration states were reestablished. Five days after the initial exposure, this series of adapted animals was loaded over the range 2.0-5.0 ml/100 g b.w. During tolerance tests on both nonadapted and adapted animals, urine was collected for a one-hour period before loading (control) and at 30, 60, and 360 minutes after loading. All samples were analyzed for sucrose(9) and total solute concentration (freezing point osmometer).

Following the 6-hour test periods, both once- and twice-loaded animals were returned to individual cages, allowed food and water freely, and were observed for the following 24 hours. Of those animals which did not survive the load, the time of death was variable between 2 and 24 hours after loading. Animals alive at the end of the 24-hour postinfusion period were considered permanent survivors.

Results. Sucrose tolerance. Survival data for nonadapted and adapted rats given increasing loads of hypertonic sucrose are shown in Fig. 1. Regression lines relating

LOAD ml 1.46M Sucrose per 100gm body wt	NON-ADAPTED Survivors / Total	% Survival	ADAPTED Survivors / Total	% Survival
2.0	13/14	93	13/13	100
2.5	13/18	72	8/8	100
3.0	7/10	70	8/9	89
3.5	4/10	40	7/9	78
4.0	3/10	30	7/10	70
4.5	0/10	0	8/10	80
5.0	—	—	3/8	38

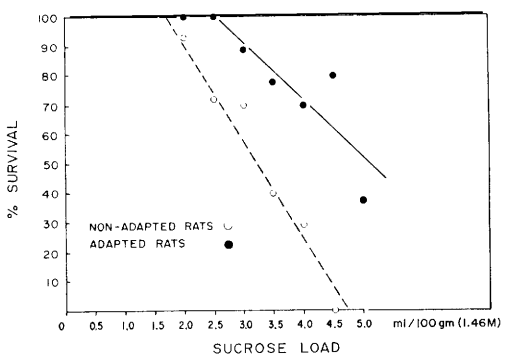

FIG. 1. Tolerance of nonadapted and adapted rats to hypertonic sucrose (1.46 M) infused through chronically indwelling arterial catheters.

survival to sucrose load were computed by the method of least squares. At all sucrose loads survival ratios were greater ($P<0.07$) in animals previously exposed to an adapting dose of sucrose (2.0 ml/100 g b.w.). From these data, the load of 1.46 M sucrose was computed which would kill one-half of the animals tested. For the nonadapted series this load would be 3.2 ml (4.7 millimoles)/100 g b.w.; for the adapted series, 5.1 ml (7.4 millimoles)/100 g b.w.

Urine flow and solute excretion. Table I gives urine flow, total solute and sucrose concentrations of nonadapted and adapted rats over time following infusion of loads between 2.0 and 4.5 ml/100 g b.w. In both series the general responses to the infused loads were similar. Urine flow (ml/100 g/min) increased sharply during the first 30 minutes after loading in both series although, in general, the increase was smaller in the adapted groups. Thereafter, urine flows in both series were more nearly the same. These data further indicate that the adapted series achieve a slightly higher total solute concentration in urine than do nonadapted animals, particularly during the final collection interval. Sucrose concentrations in urine generally were similar in both the nonadapted and adapted series.

A more pertinent analysis of the excretion response of nonadapted and adapted animals to increasing sucrose loads was made by comparing the mass flow of total solutes and sucrose within each collection interval (Table II). During the 30-minute interval following infusion the mass flow of sucrose and total solutes decrease slightly in nonadapted rats as the load is increased. In contrast, adapted animals show a slightly increasing rate of excretion of both sucrose and total solutes with increasing sucrose loads, although the rate of solute (and sucrose) excretion was initially lower in this series. During this interval sucrose represents approximately $\frac{2}{3}$ of the total solute excretion. This ratio is maintained even as the infused load is increased and does not appear to differ between nonadapted and adapted rats. In the second 30-minute interval (30 to 60 min) the rate of solute excretion is greater in adapted animals, but the general response in both series is similar. With increasing loads, rates of excretion of solutes and sucrose increase, then decrease beyond loads of 3.5 and 4.0 ml/100 g b.w. During this time sucrose makes up about $\frac{3}{4}$ of the solute excretion at all loads in both nonadapted and adapted animals. In the final interval (60 to 360 min) sucrose and solute excretion are comparable between the nonadapted and adapted animals at all loads and show a small increase in rate as the loads increase. Sucrose to total solute ratio varies during this interval from approximately 0.4 to 0.8. The smaller fractions calculated during this interval reflect the more nearly complete recovery of infused sucrose within the first 60 minutes after loading at 2.0 and 2.5 ml/100 g b.w., thereby limiting the availability of sucrose for excretion in the final collection interval.

During the period of greatest diuretic activity (within the first hour after loading) urine flow in the nonadapted animals decreases as the load is increased (Table III). The adapted animals, however, increase urine flow with increasing loads, although the initial flow was lower than that of the corresponding nonadapted group. This difference in the urine flow response of nonadapted and adapted animals is reflected by the total sucrose excreted during the same collection interval (Table III).

Discussion. From the standpoint of tolerance, rats previously infused with hypertonic sucrose (adapted) are better able to withstand the damaging effects of large doses of sucrose than are normal (nonadapted) rats. The present data support similar findings for rats adapted to sucrose by intraperitoneal infusion(3). It is suggested that the increased resistance of the adapted rat represents an enhanced "tissue tolerance" for the disrupting effects of the disaccharide although the present study does not allow for the selection of a critical tissue(s). This suggestion is based on the finding that at all loads between 2.0 and 3.5 ml/100 g b.w. the adapted rats retain a greater quantity of sucrose (at any given time following infusion) than do the nonadapted counterparts, yet are better able to tolerate the condition.

TABLE I. Urine Flow ($\dot{V}u$; ml/100 g/Min), Osmolal Concentration (Uosm; mOsm/kg H_2O), and Sucrose Concentration (Us; mM/l) After Infusion of Hypertonic Sucrose in Nonadapted (NA) and Adapted (A) Rats.

Sucrose load, ml/100 g b.w. (mM/100 g b.w.)	−60 to 0 min (control)			0 to 30 min			30 to 60 min			60 to 360 min		
	NA	A	P	NA	A	P	NA	A	P	NA	A	P
2.0 (2.92)	(13)	(13)		(13)	(13)		(13)	(13)		(12)	(12)	
$\dot{V}u$	.024 ±.009	.014 ±.006	<.05	.207 ±.029	.113 ±.023	<.05	.039 ±.010	.056 ±.008	<.05	.005 ±.002	.004 ±.001	>.05
Uosm	560 ± 228	673 ± 442	>.05	414 ± 33	476 ± 40	<.05	600 ± 67	625 ± 34	>.05	1014 ± 225	1234 ± 184	<.05
Us	—	—	—	255 ± 21	298 ± 25	<.05	443 ± 50	426 ± 24	>.05	429 ± 83	428 ± 46	>.05
2.5 (3.65)	(13)	(8)		(13)	(8)		(13)	(8)		(13)	(8)	
$\dot{V}u$	.025 ±.011	.016 ±.006	>.05	.174 ±.048	.125 ±.022	<.05	.057 ±.016	.060 ±.009	>.05	.006 ±.001	.006 ±.001	>.05
Uosm	510 ± 254	479 ± 156	>.05	429 ± 26	449 ± 21	>.05	591 ± 36	595 ± 23	>.05	924 ± 166	1079 ± 93	<.05
Us	—	—	—	274 ± 25	301 ± 15	<.05	430 ± 26	429 ± 18	>.05	455 ± 52	449 ± 33	>.05
3.0 (4.38)	(8)	(8)		(8)	(8)		(8)	(8)		(8)	(8)	
$\dot{V}u$	.018 ±.010	.015 ±.004	>.05	.173 ±.037	.124 ±.025	<.05	.075 ±.004	.076 ±.013	>.05	.010 ±.001	.008 ±.001	<.05
Uosm	620 ± 469	576 ± 77	>.05	434 ± 19	454 ± 18	<.05	545 ± 34	566 ± 23	>.05	585 ± 119	806 ± 120	>.05
Us	—	—	—	291 ± 32	294 ± 22	>.05	420 ± 29	420 ± 28	>.05	487 ± 24	478 ± 27	>.05
3.5 (5.11)	(7)	(8)		(7)	(8)		(7)	(8)		(7)	(8)	
$\dot{V}u$	.028 ±.013	.016 ±.009	>.05	.145 ±.024	.123 ±.014	<.05	.064 ±.014	.075 ±.014	>.05	.014 ±.002	.012 ±.001	<.05
Uosm	438 ± 246	549 ± 205	>.05	442 ± 18	464 ± 17	<.05	514 ± 45	555 ± 14	<.05	571 ± 53	738 ± 62	<.05
Us	—	—	—	299 ± 22	303 ± 24	>.05	414 ± 28	416 ± 11	>.05	428 ± 36	455 ± 32	>.05
4.0 (5.84)	(10)	(9)		(10)	(9)		(10)	(9)		(8)	(9)	
$\dot{V}u$	.025 ±.015	.016 ±.008	>.05	.143 ±.029	.140 ±.034	>.05	.063 ±.023	.088 ±.025	<.05	.015 ±.002	.014 ±.003	>.05
Uosm	430 ± 224	541 ± 218	>.05	463 ± 46	471 ± 30	>.05	523 ± 28	546 ± 25	>.05	589 ± 54	704 ± 78	<.05
Us	—	—	—	328 ± 41	319 ± 22	>.05	412 ± 26	416 ± 24	>.05	437 ± 36	468 ± 19	<.05
4.5 (6.57)	(7)	(9)		(7)	(9)		(7)	(9)		(1)	(8)	
$\dot{V}u$	.028 ±.008	.015 ±.006	<.05	.132 ±.029	.159 ±.025	>.05	.050 ±.023	.072 ±.022	>.05	.014	.015 ±.002	>.05
Uosm	363 ± 127	640 ± 161	<.05	439 ± 20	487 ± 23	<.05	509 ± 19	545 ± 42	>.05	520	667 ± 47	<.05
Us	—	—	—	313 ± 27	332 ± 14	>.05	398 ± 22	423 ± 16	<.05	397	465 ± 15	<.05

Values are means ± S.D. Figures in parentheses are numbers of animals per group. Sucrose infused as a 1.46 M (50% $^{w}/_{v}$) solution in all animals through chronically indwelling arterial catheters.

TABLE II. Total Solute and Sucrose Excretion After Infusion of Hypertonic Sucrose in Nonadapted (NA) and Adapted (A) Rats.

Sucrose load, ml/100 g b.w. (mM/100 g b.w.)	0 to 30 min						30 to 60 min						60 to 360 min					
	Sucrose excretion,* μM/100 g/min		Total solute excretion,† μOsm/100 g /min		$\frac{(\dot{V}u)(Us)}{(\dot{V}u)(Uosm)}$		Sucrose excretion,* μM/100 g/min		Total solute excretion,† μOsm/100 g /min		$\frac{(\dot{V}u)(Us)}{(\dot{V}u)(Uosm)}$		Sucrose excretion, μM/100 g/min		Total solute excretion, μOsm/100 g /min		$\frac{(\dot{V}u)(Us)}{(\dot{V}u)(Uosm)}$	
	NA	A	NA	A	NA	A	NA	A	NA	A	NA	A	NA	A	NA	A	NA	A
2.0 (2.92)	52.78	33.67	85.70	53.79	.62	.62	17.28	23.86	23.40	35.00	.74	.68	2.14	1.71	5.07	4.94	.42	.35
2.5 (3.65)	47.68	37.62	74.65	56.12	.64	.67	24.51	25.74	33.69	35.70	.73	.72	2.73	2.69	5.54	6.47	.49	.42
3.0 (4.38)	50.34	36.46	75.08	56.30	.67	.65	31.50	31.92	40.88	43.02	.77	.74	4.87	3.82	5.85	6.45	.83	.59
3.5 (5.11)	43.36	37.27	64.09	57.07	.68	.65	26.50	31.20	32.90	41.62	.80	.75	5.99	5.46	7.99	8.86	.75	.62
4.0 (5.84)	46.90	44.66	66.21	65.94	.71	.68	25.96	36.61	32.95	48.05	.79	.76	6.56	6.55	8.84	9.86	.74	.66
4.5 (6.57)	41.32	51.20	57.95	77.43	.71	.66	19.90	30.46	25.45	39.24	.78	.78	5.56	6.98	7.28	10.00	.76	.70

* (ml/100 g/min; $\dot{V}u$) (μM/ml; Us). † (ml/100 g/min; $\dot{V}u$) (μOsm/g H_2O; Uosm).

Although it seems clear that the kidney is implicated in the adaptation described it has not yet been established whether the kidney itself is undergoing an adaptation or is merely reflecting an adaptation of some other system. The role of the kidney in the adaptation described may be inferred from the patterns in solute and sucrose excretion with increasing sucrose loads and the differences in excretion between nonadapted and adapted animals. Assuming that sucrose given intraarterially is cleared from the blood only by glomerular filtration, that tubular reabsorption is minimal, and further that parenteral sucrose is not metabolized, then rate of excretion of sucrose is the product of the plasma sucrose concentration and the sucrose clearance. If the time course for distribution is nearly the same for all loads of sucrose administered, then plasma concentration should be nearly proportional to the load given (shortly after infusion) and the rate of sucrose excretion proportional to the plasma concentration of sucrose (and the GFR). Since increasing loads of sucrose in the nonadapted animal (during the first 30 minutes) are accompanied by a slightly decreasing rate of sucrose excretion, GFR is depressed as the load increases. In adapted animals, given the same set of assumptions, increasing loads are accompanied by a slight increase in sucrose excretion though not in proportion to the increase in load. It is evident from the disparity in the rate of sucrose excretion of nonadapted and adapted groups at the smallest load, that GFR of adapted animals is only about 60% that of nonadapted animals during the first 30 minutes after infusion. At the highest load (4.5 ml/100 g b.w.) GFR of the adapted group is 125% that of the nonadapted animals.

These data suggest that increasing loads of hypertonic sucrose suppress the GFR in nonadapted rats. This response may persist as long as 5 days after the initial loading, but when again infused with the same loads, the now adapted rats appear less susceptible to the GFR depressing action of the hypertonic loads, particularly at the higher doses. The persistence of a lowered GFR is further suggested by the generally lower urine flow (and

TABLE III. Total Sucrose Excretion, Urine Volume and Urinary Sucrose Concentration During the First Hour After Loading (NA, Nonadapted Rats; A, Adapted Rats).

Sucrose load (ml/100 g b.w.)	Sucrose excreted 0-60 min (mM/100 g)		Urine volume 0-60 min (ml/100 g)		Urine sucrose concentration (mM/l)	
	NA	A	NA	A	NA	A
2.0	2.11 (13)	1.74 (13)	7.4	5.1	285	341
2.5	2.16 (13)	1.93 (8)	6.9	5.6	313	345
3.0	2.44 (8)	2.05 (8)	7.4	6.0	330	342
3.5	2.11 (7)	2.08 (8)	6.3	6.0	335	347
4.0	2.19 (10)	2.42 (9)	6.2	6.8	353	356
4.5	1.85 (7)	2.52 (9)	5.5	7.0	336	360

Values are means. Figures in parentheses are numbers of animals per group. Sucrose infused as a 1.46 M (50% $^{w}/_{v}$) solution through chronically indwelling arterial catheters.

total solute excretion) in adapted animals during the second control interval (Table I).

Summary. Two series of unanesthetized rats were infused intraarterially with standardized volumes of 1.46 M (50% w/v) sucrose over the range 2.0 to 5.0 ml/100 g body weight. Animals in one of these series had been exposed 5 days earlier to the same concentration of sucrose at 2.0 ml/100 g body weight. These latter animals constituted the adapted groups. Comparison of the sucrose tolerance of adapted animals with nonadapted revealed that previous exposure to hypertonic sucrose significantly increased the resistance of twice-loaded animals to the damaging effects of the hypertonic solution. Evaluation of the excretion patterns of urinary solutes and the relationships between urine flow and solute concentrations suggest that a reduction in GFR may occur in nonadapted animals as load of hypertonic sucrose is increased from 2.0 to 4.5 ml/100 g b.w. Similar loads given to adapted animals appear less effective in their GFR depressing actions.

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1. Helmholz, H. F., J. Pediatr., 1933, v3, 144.
2. Lindberg, H. A., Wald, M. H., Barker, M. H., Arch. Int. Med., 1939, v63, 907.
3. Iampietro, P. F., Am. J. Physiol., 1956, v184, 390.
4. Anderson, W. A. D., Bethea, W. R., Jr., J. Am. Med. Assn., 1940, v114, 1983.
5. Allen, A. C., The Kidney, Grune and Stratton, New York, 1962, p324.
6. Fiorica, V., Iampietro, P. F., deSteiguer, D., Morrison, R. D., Proc. Soc. Exp. Biol. and Med., 1965, v118, 594.
7. Fiorica, V., Iampietro, P. F., Moses, R., Can. J. Physiol. Pharmacol., 1966, in press.
8. Adolph, E. F., Barker, J. P., Hoy, P. A., Am. J. Physiol., 1954, v178, 538.
9. Schreiner, G. E., Proc. Soc. Exp. Biol. and Med., 1950, v74, 117.

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Carbohydrate and Lipid Metabolism in Animals Treated with Pyrrolidinomethyl Tetracycline. (31217)

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Utilization of glucose is disturbed in animals after prolonged administration of penicillin(1), dihydrostreptomycin(2), oxytetracycline(3), chlortetracycline(4), and chloramphenicol(5). A mixture of penicillin and streptomycin when administered to rats and rabbits did not affect fasting blood sugar or glucose tolerance(6). Deposition of glycogen in liver was diminished in rats after treatment with oxytetracycline(3) and chlortetra-

* Work was most carried out at S. M. S. Medical College, Jaipur, India.